

sham-controlled randomized trial and is approved in the United States. In **chronic migraine** (at least 15 days per month with headaches lasting 4 hours per day or longer), acupuncture is as effective as prophylactic pharmacologic treatment, and botulinum toxin type A reduces headache frequency. Certain neurostimulation techniques look promising as preventive treatment as well as having a role in treatment of acute attacks. These include single-pulse transcranial magnetic stimulation, vagus nerve stimulators, and implantable occipital nerve stimulation, but critical appraisal is necessary.

2. Tension-Type Headache

This is the most common type of primary headache disorder. Patients frequently complain of pericranial tenderness, poor concentration, and other nonspecific symptoms, in addition to headaches that are often vise-like or tight in quality but not pulsatile. Headaches may be exacerbated by emotional stress, fatigue, noise, or glare. The headaches are usually generalized, may be most intense about the neck or back of the head, and are not associated with focal neurologic symptoms. There is diagnostic overlap with migraine.

The therapeutic approach is similar to that in migraine, except that triptans and ergotamines are *not* indicated. Tricyclic antidepressants, such as amitriptyline, are supported for headache prophylaxis by randomized trial evidence and often are tried first. Treatment of comorbid anxiety or depression is important. Behavioral therapies that may be effective include biofeedback and relaxation training.

3. Cluster Headache

Cluster headache affects predominantly middle-aged men. The pathophysiology is unclear but may relate to activation of cells in the ipsilateral hypothalamus, triggering the trigeminal autonomic vascular system. There is often no family history of headache or migraine. Episodes of severe unilateral periorbital pain occur daily for several weeks and are often accompanied by one or more of the following: ipsilateral nasal congestion, rhinorrhea, lacrimation, redness of the eye, and Horner syndrome (ptosis, pupillary meiosis, and facial anhidrosis or hypohidrosis). During attacks, patients are often restless and agitated. Episodes typically occur at night, awaken the patient, and last between 15 minutes and 3 hours. Spontaneous remission then occurs, and the patient remains well for weeks or months before another bout of closely spaced attacks. Bouts may last for 4 to 8 weeks and may occur up to several times per year. During a bout, many patients report alcohol triggers an attack; others report that stress, glare, or ingestion of specific foods occasionally precipitates attacks. In occasional patients, remission does not occur. This variant has been referred to as **chronic cluster headache**. In longstanding cases, Horner syndrome may persist between attacks.

Cluster headache is one of the **trigeminal autonomic cephalgias**, which include hemicrania continua, paroxysmal hemicrania, and short-lasting neuralgiform headache attacks with conjunctival injection and tearing. Similar to cluster headache, the other trigeminal

autonomic cephalgias consist of unilateral periorbital pain associated with ipsilateral autonomic symptoms; they are distinguished from cluster headache by different attack duration and frequency and their exquisite responsiveness to indomethacin.

Treatment of an individual attack with oral medications is generally unsatisfactory, but subcutaneous (6 mg) or intranasal (20 mg/spray) sumatriptan or inhalation of 100% oxygen (12–15 L/min for 15 minutes via a non-rebreather mask) may be effective. Zolmitriptan (5- and 10-mg nasal spray) is also effective. Dihydroergotamine (0.5–1 mg intramuscularly or intravenously) or viscous lidocaine (1 mg of 4–6% solution intranasally) is sometimes effective.

Various prophylactic agents include oral medications such as lithium carbonate (start at 300 mg daily, titrating according to serum levels and treatment response up to a typical total daily dose of 900–1200 mg, divided three or four times), verapamil (start at 240 mg daily, increase by 80 mg every 2 weeks to 960 mg daily, with routine ECG to monitor the PR interval), topiramate (100–400 mg daily), and civamide (not available in the United States). As there is often a delay before these medications are effective, transitional therapy is often used. Prednisone (60 mg daily for 5 days followed by gradual withdrawal over 7–10 days) is effective in 70–80% of patients, and suboccipital corticosteroid injection about the greater occipital nerve is effective in 75%. Ergotamine tartrate can be given as rectal suppositories (0.5–1 mg at night or twice daily), by mouth (2 mg daily), or by subcutaneous injection (0.25 mg three times daily for 5 days per week). Electrical stimulation of the vagus nerve at headache onset successfully aborts pain in 30–50% of attacks, and twice daily prophylactic stimulation reduces attack number in chronic cluster headache; this treatment is approved in the United States. In Europe, sphenopalatine ganglion stimulation is approved for treatment of cluster headache based on efficacy in one randomized sham-controlled study. Limited evidence suggests that electrical stimulation of the occipital nerve by an implantable device may be helpful, especially in chronic cluster headache.

4. Posttraumatic Headache

A variety of nonspecific symptoms may follow closed head injury, regardless of whether consciousness is lost (see Head Injury). Headache is often a conspicuous feature. It usually appears within a day or so following injury, may worsen over the ensuing weeks, and then gradually subsides. It is usually a constant dull ache, with superimposed throbbing that may be localized, lateralized, or generalized. Headaches are sometimes accompanied by nausea, vomiting, or scintillating scotomas and often respond to simple analgesics; severe headaches may necessitate preventive treatment as outlined for migraine.

5. Primary Cough Headache

Severe head pain may be produced by coughing (and by straining, sneezing, and laughing) but, fortunately, usually lasts for only a few minutes or less. Intracranial lesions, usually in the posterior fossa (eg, Arnold-Chiari

malformation), are present in about 10% of cases, and brain tumors or other space-occupying lesions may present in this way. Accordingly, *CT scanning or MRI should be undertaken in all patients.*

The disorder is usually self-limited, although it may persist for several years. For unknown reasons, symptoms sometimes clear completely after lumbar puncture. Indomethacin (75–150 mg daily orally) may provide relief. Similar activity-triggered headache syndromes include primary exertional headache and primary headache associated with sexual activity.

6. Headache Due to Giant Cell (Temporal or Cranial) Arteritis

This topic is discussed in Chapter 20.

7. Headache Due to Intracranial Mass Lesion

Intracranial mass lesions of all types may cause headache owing to displacement of vascular structures and other pain-sensitive tissues. While pain and location are nonspecific, headache may be worse upon lying down, awaken the patient at night, or peak in the morning after overnight recumbency. *The key feature prompting brain imaging is a new or worsening headache in middle or later life.* Other features suggesting an intracranial lesion include signs or symptoms of infection or malignancy such as fever, night sweats, and weight loss; immunocompromise; or history of malignancy. Signs of focal or diffuse cerebral dysfunction or of increased intracranial pressure (eg, papilledema) also necessitate investigation.

8. Medication Overuse (Analgesic Rebound) Headache

In many patients with **chronic daily headaches**, medication overuse is responsible. Patients have chronic pain or severe headache unresponsive to medication (typically defined as no effect after having been used regularly for more than 3 months). Ergotamines, triptans, medications containing butalbital, and opioids cause medication overuse headache when taken on more than 10 days per month; acetaminophen, acetylsalicylic acid, and nonsteroidal anti-inflammatory drugs may also be offenders if taken on more than 15 days per month. Early initiation of a migraine preventive therapy permits withdrawal of analgesics and eventual relief of headache.

9. Headache Due to Other Neurologic Causes

Cerebrovascular disease may be associated with headache, but the mechanism is unclear. Headache may occur with internal carotid artery occlusion or carotid dissection and after carotid endarterectomy. Acute severe headache (“**thunderclap**”) accompanies subarachnoid hemorrhage, carotid or vertebral artery dissection, cerebral venous thrombosis, ischemic or hemorrhagic stroke, reversible cerebral vasoconstriction syndrome, hypertensive crisis, posterior reversible leukoencephalopathy syndrome, pituitary apoplexy, spontaneous intracranial hypotension, vasculitis, and meningeal infections; accompanying focal

neurologic signs, impairment of consciousness, and signs of meningeal irritation indicate the need for further investigations. Headaches are also a feature of idiopathic intracranial hypertension (pseudotumor cerebri).

Dull or throbbing headache is a frequent sequela of lumbar puncture and may last for several days. It is aggravated by the erect posture and alleviated by recumbency. The mechanism is unclear, but the headache is commonly attributed to leakage of cerebrospinal fluid through the dural puncture site. Its incidence may be reduced if an atraumatic needle (instead of a beveled, cutting needle) is used for the lumbar puncture.

► When to Refer

- Thunderclap onset.
- Increasing headache unresponsive to simple measures.
- History of trauma, hypertension, fever, visual changes.
- Presence of neurologic signs or of scalp tenderness.

► When to Admit

Suspected subarachnoid hemorrhage or other structural intracranial lesion.

Ceriani CEJ et al. Novel medications for the treatment of migraine. *Headache.* 2019;59:1597. [PMID: 31559638]

Vukovic-Cvetkovic V et al. Neurostimulation for the treatment of chronic migraine and cluster headache. *Acta Neurol Scand.* 2019;139:4. [PMID: 30291633]

FACIAL PAIN

1. Trigeminal Neuralgia



ESSENTIALS OF DIAGNOSIS

- ▶ Brief episodes of stabbing facial pain.
- ▶ Pain is in the territory of the second and third division of the trigeminal nerve.
- ▶ Pain exacerbated by touch.

► General Considerations

Trigeminal neuralgia (“tic douloureux”) is most common in middle and later life. It affects women more frequently than men. Pain may be due to an anomalous artery or vein impinging on the trigeminal nerve.

► Clinical Findings

Momentary episodes of sudden lancinating facial pain commonly arise near one side of the mouth and shoot toward the ipsilateral ear, eye, or nostril. The pain may be triggered by such factors as touch, movement, drafts, and eating. In order to lessen the likelihood of triggering further attacks, many patients try to hold the face still while talking. Spontaneous remissions for several months or

longer may occur. As the disorder progresses, however, the episodes of pain become more frequent, remissions become shorter and less common, and a dull ache may persist between the episodes of stabbing pain. Symptoms remain confined to the distribution of the trigeminal nerve (usually the second or third division) on one side only.

Differential Diagnosis

The characteristic features of the pain in trigeminal neuralgia usually distinguish it from other causes of facial pain. Neurologic examination shows no abnormality except in a few patients in whom trigeminal neuralgia is symptomatic of some underlying lesion, such as multiple sclerosis or a brainstem neoplasm, in which case the finding will depend on the nature and site of the lesion. Multiple sclerosis must

be suspected in a patient younger than 40 years in whom trigeminal neuralgia is the presenting symptom, even if there are no other neurologic signs. Bilateral symptoms should also prompt further investigation. Brain MRI need only be obtained when a secondary cause is suspected; it is usually normal in classic trigeminal neuralgia.

Treatment

The medications most helpful for treatment are oxcarbazepine (although not approved by the FDA for this indication) or carbamazepine, with monitoring by serial blood counts and liver biochemical tests. If these medications are ineffective or cannot be tolerated, phenytoin should be tried. (Doses and side effects of these medications are shown in Table 24–2.) Baclofen (10–20 mg orally three or

Table 24–2. Medication treatment for seizures in adults (in alphabetical order within classes).

Medication	Usual Adult Daily Oral Dose	Minimum No. of Daily Doses	Time to Steady-State Medication Levels	Optimal Medication Level and Laboratory Monitoring ¹	Selected Side Effects and Idiosyncratic Reactions
Generalized or Focal Seizures					
Brivaracetam ^{2,3}	50–100 mg	2	1–2 days	CBC, liver biochemical tests	Somnolence, fatigue, ataxia, vertigo, psychosis, leukopenia, hypersensitivity (bronchospasm and angioedema).
Cannabidiol ⁴	5–20 mg/kg	2	11–13 days	Liver biochemical tests at baseline, 1, 3, and 6 months	Somnolence, fatigue, anorexia, weight loss, anemia, diarrhea, rash, sleep disorder, infections. Elevation in liver enzymes may occur; reduce dose in hepatic impairment.
Carbamazepine ²	400–1600 mg (immediate or extended release)	2	3–4 days	4–8 mcg/mL CBC, liver biochemical tests, BUN/Cr	Nystagmus, dysarthria, diplopia, ataxia, drowsiness, nausea, blood dyscrasias, hepatotoxicity, hyponatremia, Stevens-Johnson syndrome. ⁵ May exacerbate myoclonic seizures.
Cenobamate ^{2,3}	200–400 mg	1	14 days	Liver biochemical tests, potassium	Multiorgan hypersensitivity, QT shortening, somnolence, dizziness, cognitive dysfunction, blurred vision.
Clobazam ⁶	10–40 mg	2	7–10 days		Lethargy and somnolence, ataxia, insomnia, dysarthria, aggression, constipation, fever, Stevens-Johnson syndrome.
Clorazepate ³	22.5–90 mg	2	10 days		Sedation, dizziness, confusion, ataxia, depression, dependency/abuse.
Eslicarbazepine ^{2,3}	400–1200 mg	1	4 days	Serum sodium and chloride; liver biochemical tests	As for carbamazepine.
Ezogabine ³	300–1200 mg	3	2–3 days	ECG to assess QT interval	Dizziness, somnolence, confusion, vertigo, nausea, ataxia, psychiatric disturbances, prolonged QT interval, retinal abnormalities. ⁷
Felbamate ^{2,3,6,8}	1200–3600 mg	3	4–5 days	CBC and reticulocytes, liver biochemical tests	Anorexia, nausea, vomiting, headache, insomnia, weight loss, dizziness, hepatotoxicity, fatal aplastic anemia. Reserved for refractory epilepsy.

(continued)

Table 24–2. Medication treatment for seizures in adults (in alphabetical order within classes). (continued)

Medication	Usual Adult Daily Oral Dose	Minimum No. of Daily Doses	Time to Steady-State Medication Levels	Optimal Medication Level and Laboratory Monitoring ¹	Selected Side Effects and Idiosyncratic Reactions
Gabapentin ³	900–3600 mg	3	1 day		Sedation, fatigue, ataxia, nystagmus, weight loss.
Lacosamide ^{2,3}	100–400 mg	2	3 days	ECG if known cardiac conduction problems or severe cardiac disease	Vertigo, diplopia, nausea, headache, fatigue, ataxia, tremor, anaphylactoid reactions, PR prolongation, cardiac dysrhythmia, suicidality.
Lamotrigine ^{3,6,9,10}	100–500 mg	2	4–5 days		Sedation, skin rash, visual disturbances, dyspepsia, ataxia.
Levetiracetam ^{3,9,11}	1000–3000 mg	2	2 days		Somnolence, ataxia, headache, behavioral changes.
Oxcarbazepine ^{2,3}	900–1800 mg	2	2–3 days	Serum sodium	As for carbamazepine.
Perampanel ^{2,3,9}	4–12 mg	1	3 weeks		Dizziness, somnolence, irritability, weight gain, falls, ataxia, dysarthria, blurred vision.
Phenobarbital ^{2,12}	100–200 mg	1	14–21 days	10–40 mcg/mL CBC, liver biochemical tests, BUN/Cr	Drowsiness, nystagmus, ataxia, skin rashes, learning difficulties, hyperactivity.
Phenytoin ^{2,12}	200–400 mg	1	5–10 days	10–20 mcg/mL CBC, liver biochemical tests, folate	Nystagmus, ataxia, dysarthria, sedation, confusion, gingival hyperplasia, hirsutism, megaloblastic anemia, blood dyscrasias, skin rashes, fever, systemic lupus erythematosus, lymphadenopathy, peripheral neuropathy, dyskinesias. May exacerbate myoclonic seizures.
Pregabalin ³	150–300 mg	2	2–4 days		Somnolence, dizziness, poor concentration, weight gain, thrombocytopenia, skin rashes, anaphylactoid reactions.
Primidone ^{2,12}	750–1500 mg	3	4–7 days	5–12 mcg/mL CBC	Sedation, nystagmus, ataxia, vertigo, nausea, skin rashes, megaloblastic anemia, irritability.
Rufinamide ⁶	800–3200 mg	2	2 days		Somnolence, headache, dizziness, suicidality, Stevens-Johnson syndrome, leukopenia, shortened QT interval, nausea, vomiting.
Tiagabine ³	32–56 mg	2	2 days		Somnolence, anxiety, dizziness, poor concentration, tremor, diarrhea.
Topiramate ^{2,3,6,9,12}	200–400 mg	2	4 days	Serum bicarbonate, BUN/Cr in elderly patients	Somnolence, nausea, dyspepsia, irritability, dizziness, ataxia, nystagmus, diplopia, glaucoma, renal calculi, weight loss, hypohidrosis, hyperthermia.
Valproic acid ^{2,3,13,14}	1500–2000 mg	2–3	2–4 days	50–100 mcg/mL CBC, liver biochemical tests	Nausea, vomiting, diarrhea, drowsiness, alopecia, weight gain, hepatotoxicity, thrombocytopenia, tremor, pancreatitis. Teratogenic; avoid in women of childbearing age.
Vigabatrin ^{3,15}	3000 mg	2	2 days		Somnolence, anorexia, nausea, vomiting, agitation, hostility, confusion, suicidality, neutropenia, Stevens-Johnson syndrome, permanent visual field loss. ⁷
Zonisamide ³	200–600 mg	1	14 days	BUN/Cr, serum bicarbonate	Somnolence, ataxia, anorexia, nausea, vomiting, rash, confusion, renal calculi. Do not use in patients with sulfonamide allergy.

(continued)

Table 24–2. Medication treatment for seizures in adults (in alphabetical order within classes). (continued)

Medication	Usual Adult Daily Oral Dose	Minimum No. of Daily Doses	Time to Steady-State Medication Levels	Optimal Medication Level and Laboratory Monitoring ¹	Selected Side Effects and Idiosyncratic Reactions
Absence Seizures					
Clonazepam ^{6,11,13,16,17}	0.04–0.2 mg/kg	2	7–10 days	20–80 ng/mL CBC, liver biochemical tests	Drowsiness, ataxia, irritability, behavioral changes, exacerbation of tonic-clonic seizures.
Ethosuximide ¹³	500–1500 mg	2	5–10 days	40–100 mcg/mL CBC, liver biochemical tests, urinalysis	Nausea, vomiting, anorexia, headache, lethargy, unsteadiness, blood dyscrasias, systemic lupus erythematosus, urticaria, pruritus.
Valproic acid ^{2,3,13,14}	1500–2000 mg	2–3	2–4 days	See above	Nausea, vomiting, diarrhea, drowsiness, alopecia, weight gain, hepatotoxicity, thrombocytopenia, tremor, pancreatitis.
Myoclonic Seizures					
Clonazepam ^{6,11,13,16,17}	0.04–0.2 mg/kg	2	7–10 days	See above	Drowsiness, ataxia, irritability, behavioral changes, exacerbation of tonic-clonic seizures.
Levetiracetam ^{3,9,11}	1000–3000 mg	2	2 days		Somnolence, ataxia, headache, behavioral changes.
Valproic acid ^{2,3,13,14}	1500–2000 mg	2–3	2–4 days	See above	Nausea, vomiting, diarrhea, drowsiness, alopecia, weight gain, hepatotoxicity, thrombocytopenia, tremor, pancreatitis.

BUN, blood urea nitrogen; CBC, complete blood count; Cr, creatinine; ECG, electrocardiogram. Note that many factors influence optimal dose of these drugs including age, tolerance, and concomitant medication.

¹Patients starting treatment with any antiepileptic drug should be monitored for new or worsening depression or suicidal thoughts, especially during the first weeks of therapy. Baseline measurement of creatinine clearance is advisable in renally metabolized drugs.

²Approved as monotherapy for focal-onset seizures.

³Approved as adjunctive therapy for focal-onset seizures.

⁴Approved for treatment of seizures in Lennox-Gastaut and Dravet syndrome in patients 2 years and older.

⁵Carriers of the HLA-B*1502 allele are at higher risk for Stevens-Johnson syndrome. Patients of Asian ancestry should be tested for this allele prior to initiation of therapy.

⁶Approved as adjunctive therapy for Lennox-Gastaut syndrome.

⁷Regular ophthalmologic examination is recommended.

⁸Not to be used as a first-line drug; when used, blood counts should be performed regularly (every 2–4 weeks). Should be used only in selected patients because of risk of aplastic anemia and hepatic failure. It is advisable to obtain written informed consent before use.

⁹Approved as adjunctive therapy for primary generalized tonic-clonic seizures.

¹⁰Approved as monotherapy (after conversion from another drug) in focal-onset seizures.

¹¹Approved as adjunctive therapy for myoclonic seizures.

¹²Approved as initial monotherapy for primary generalized tonic-clonic seizures.

¹³Approved as monotherapy and adjunctive therapy for absence seizures.

¹⁴Approved as adjunctive therapy for patients with multiple seizure types including absence seizures.

¹⁵Approved as monotherapy for infantile spasms.

¹⁶Approved as monotherapy for Lennox-Gastaut syndrome.

¹⁷Approved as monotherapy for myoclonic seizures.

four times daily), topiramate (50 mg orally twice daily), or lamotrigine (400 mg orally daily) may also be helpful, either alone or in combination with one of these other agents. Gabapentin may also relieve pain, especially in patients who do not respond to conventional medical therapy and those with multiple sclerosis. Depending on response and tolerance, up to 3600 mg daily orally is given in divided doses.

For neuralgia refractory to medical treatment, several surgical treatment options are available that provide initial pain relief in at least 80% of patients. Microvascular

surgical decompression with separation of the anomalous vessel (usually not visible on CT scans, MRI, or arteriograms) from the nerve root produces long-term relief of symptoms in roughly 75% of patients. Three less invasive techniques are based on destruction of nociceptive trigeminal nerve fibers, which causes sensory loss in addition to symptom relief in half of patients: (1) radiofrequency rhizotomy produces long-term pain relief in 60% of patients, (2) percutaneous balloon compression of the trigeminal ganglion in 67%, and (3) stereotactic radiosurgery

to the trigeminal nerve root in 45%. In elderly patients with a limited life expectancy, radiofrequency rhizotomy and stereotactic radiosurgery are sometimes preferred because both can be performed without general anesthesia and have few complications. Surgical exploration is inappropriate in patients with trigeminal neuralgia due to multiple sclerosis, but the less invasive techniques are sometimes helpful.

2. Atypical Facial Pain

Facial pain without the typical features of trigeminal neuralgia is generally a constant, often burning pain that may have a restricted distribution at its onset but soon spreads to the rest of the face on the affected side and sometimes involves the other side, the neck, or the back of the head as well. The disorder is especially common in middle-aged women, many of them depressed, but it is not clear whether depression is the cause of or a reaction to the pain. Simple analgesics should be given a trial, as should tricyclic antidepressants, carbamazepine, oxcarbazepine, and phenytoin; the response is often disappointing. Opioid analgesics pose a danger of addiction. Attempts at surgical treatment are not indicated.

3. Glossopharyngeal Neuralgia

Glossopharyngeal neuralgia is an uncommon disorder in which pain similar in quality to that in trigeminal neuralgia occurs in the throat, about the tonsillar fossa, and sometimes deep in the ear and at the back of the tongue. The pain may be precipitated by swallowing, chewing, talking, or yawning and is sometimes accompanied by syncope. In most instances, no underlying structural abnormality is present; multiple sclerosis is sometimes responsible. Oxcarbazepine and carbamazepine are the treatments of choice and should be tried before any surgical procedures are considered. Microvascular decompression is often effective and is generally preferred over destructive surgical procedures such as partial rhizotomy in medically refractory cases.

4. Postherpetic Neuralgia

Postherpetic neuralgia develops in about 15% of patients who have herpes zoster (shingles). This complication seems especially likely to occur in elderly or immunocompromised persons, when the rash is severe, and when the first division of the trigeminal nerve is affected. It also relates to the duration of the rash before treatment is instituted. A history of shingles and the presence of cutaneous scarring resulting from shingles aid in the diagnosis. Severe pain with shingles correlates with the intensity of postherpetic symptoms.

Acyclovir (800 mg five times daily) or valacyclovir (1000 mg three times daily), when given within 72 hours of rash onset, reduces the incidence of postherpetic neuralgia by almost half; systemic corticosteroids do *not* help prevent postherpetic neuralgia (see Chapter 6). Management of the established complication is with simple analgesics. If they fail to help, a trial of a tricyclic antidepressant (eg, amitriptyline or nortriptyline, up to 100–150 mg daily orally) is

often effective. Other patients respond to gabapentin (up to 3600 mg daily orally) or pregabalin (up to 600 mg/daily orally). Subcutaneous injection of botulinum toxin A into the affected region produced sustained pain relief in 87% of patients in a small placebo-controlled trial. Topical application of capsaicin cream may be helpful, as may topical lidocaine (5%). The administration of **recombinant zoster vaccine** to patients over the age of 50 years is important in reducing the likelihood of herpes zoster or reducing the severity of postherpetic neuralgia should a reactivation occur.

5. Facial Pain Due to Other Causes

Facial pain may be caused by temporomandibular joint dysfunction in patients with malocclusion, abnormal bite, or faulty dentures. There may be tenderness of the masticatory muscles, and sometimes pain begins at the onset of chewing. This pattern differs from that of jaw (masticatory) claudication, a symptom of giant cell arteritis, in which pain develops progressively with mastication. Treatment of the underlying joint dysfunction relieves symptoms.

A relationship of facial pain to chewing or temperature changes may suggest a dental disturbance. The cause is sometimes not obvious, and diagnosis requires careful dental examination and radiographs. Sinusitis and ear infections causing facial pain are usually recognized by a history of respiratory tract infection, fever, and, in some instances, nasal or aural discharge. There may be localized tenderness. Radiologic evidence of sinus infection or mastoiditis is confirmatory.

Glaucoma is an important ocular cause of facial pain, usually localized to the periorbital region.

On occasion, pain in the jaw may be the principal manifestation of angina pectoris. Precipitation by exertion and radiation to more typical areas suggests a cardiac origin.

► When to Refer

- Worsening pain unresponsive to simple measures.
- Continuing pain of uncertain cause.
- For consideration of surgical treatment (trigeminal or glossopharyngeal neuralgia).

Bendtsen L et al. Advances in diagnosis, classification, pathophysiology, and management of trigeminal neuralgia. Lancet Neurol. 2020;19:784. [PMID: 32822636]

EPILEPSY



ESSENTIALS OF DIAGNOSIS

- Recurrent unprovoked seizures.
- Characteristic electroencephalographic changes accompany seizures.
- Mental status abnormalities or focal neurologic symptoms may persist for hours postictally.

► General Considerations

The term “epilepsy” denotes any disorder characterized by *recurrent unprovoked seizures*. A seizure is a transient disturbance of cerebral function due to an abnormal paroxysmal neuronal discharge in the brain. Epilepsy is relatively common, affecting approximately 0.5% of the population in the United States.

Patients with recurrent seizures provoked by a readily reversible cause, such as withdrawal from alcohol or drugs, hypoglycemia, hyperglycemia, or uremia, are not considered to have epilepsy.

► Classification of Epilepsy

According to the International League Against Epilepsy classification system, recurrent seizures should be classified first by seizure type, second by epilepsy type, and third, if possible, by epilepsy syndrome. The etiology of recurrent seizures should be sought at each stage of classification (see Etiology of Epilepsy).

A. Seizure Types

The International League Against Epilepsy distinguishes seizures affecting only part of the brain (focal seizures) from those that are generalized.

1. Focal onset seizures—The initial clinical and electroencephalographic manifestations of focal (partial) seizures indicate that only a restricted part of one cerebral hemisphere has been activated. The ictal manifestations depend on the area of the brain involved. Focal seizures are classified by motor or nonmotor onset as well as by whether awareness is impaired.

A. MOTOR VERSUS NONMOTOR ONSET—Seizures with motor onset may be **clonic, tonic, atonic, myoclonic, or hyperkinetic**, or may manifest as **automatisms** or **epileptic spasms**. The most commonly observed focal motor seizures consist of clonic jerking or automatisms. Nonmotor seizures may be manifested by sensory symptoms (eg, paresthesias or tingling, gustatory, olfactory, visual or auditory sensations), behavior arrest, cognitive symptoms (eg, speech arrest, *déjà vu*, *jamais vu*), emotional symptoms (eg, fear), or autonomic symptoms or signs (eg, abnormal epigastric sensations, sweating, flushing, pupillary dilation). Focal sensory and motor seizures may spread (or “march”) to different parts of the limb or body depending on their cortical representation and were previously called “simple partial” seizures.

B. AWARE VERSUS IMPAIRED AWARENESS—Awareness is defined as knowledge of self and environment and of events occurring during a seizure. Impaired awareness may be preceded, accompanied, or followed by the various motor and nonmotor symptoms mentioned above. Such seizures were previously called “complex partial” seizures.

C. FOCAL TO BILATERAL TONIC-CLONIC—Focal seizures sometimes involve loss of awareness and evolve to bilateral tonic-clonic seizures, in a process previously called “secondary generalization.”

2. Generalized onset seizures—Generalized seizures are thought to originate in or rapidly spread to involve bilateral cortical networks. In some cases, the distinction between focal and generalized onset can only be made by electroencephalogram (EEG). Generalized seizures are classified into those with motor or nonmotor features. Awareness is typically lost with generalized seizures but may be retained partially in the briefest absence attacks and some myoclonic seizures.

A. NONMOTOR (ABSENCE) SEIZURES—These are characterized by impairment of consciousness, sometimes with mild clonic, tonic, myoclonic, or atonic components (ie, reduction or loss of postural tone), autonomic components (eg, enuresis), or accompanying automatisms. Onset and termination of attacks are abrupt. If attacks occur during conversation, the patient may miss a few words or may break off in midsentence for a few seconds. The impairment of external awareness is so brief that the patient is unaware of it. **Absence (“petit mal”) seizures** almost always begin in childhood and frequently cease by the age of 20 years or are then replaced by other forms of generalized seizure. Electroencephalographically, such attacks are associated with bursts of bilaterally synchronous and symmetric 3-Hz spike-wave activity. A normal background in the electroencephalogram and normal or above-normal intelligence imply a good prognosis for the ultimate cessation of these seizures. **Atypical absence seizures** may demonstrate more marked changes in tone, or attacks may have a more gradual onset and termination than in typical absence seizures. They commonly occur in patients with multiple seizure types, may be accompanied by developmental delay or mental retardation, and are associated with slower spike-wave discharges than those in typical absence attacks.

B. MOTOR SEIZURES—Types of generalized motor seizures include **tonic-clonic, clonic, tonic, myoclonic, myoclonic-tonic-clonic, myoclonic-ataxic, atonic, and epileptic spasms**. During tonic-clonic seizures there is sudden loss of consciousness, the patient becomes rigid and falls to the ground, and respiration is arrested. This tonic phase, which usually lasts for under 1 minute, is followed by a clonic phase in which there is jerking of the body musculature that may last for 2 or 3 minutes and is then followed by a stage of flaccid coma. During the seizure, the tongue or lips may be bitten, urinary or fecal incontinence may occur, and the patient may be injured. Immediately after the seizure, the patient may recover consciousness, drift into sleep, have a further convulsion without recovery of consciousness between the attacks (**status epilepticus**), or after recovering consciousness have a further convolution (**serial seizures**). In other cases, patients may behave in an abnormal fashion in the immediate postictal period, without subsequent awareness or memory of events (**postepileptic automatism**). Headache, disorientation, confusion, drowsiness, nausea, soreness of the muscles, or some combination of these symptoms commonly occurs postictally. Myoclonic seizures consist of single or multiple myoclonic jerks. Atonic seizures consist of very brief (less than 2 seconds) loss of muscle tone and often result in falls (**epileptic drop attacks**). **Epileptic spasms** are sudden flexion or

extension of truncal muscles; these seizures usually manifest during infancy.

3. Unknown onset seizures—In some circumstances, seizures cannot be classified because of incomplete information or because they do not fit into any category. Generally, with additional information from the history or from video-EEG telemetry, the seizure onset can be correctly classified.

B. Epilepsy Types

The International League Against Epilepsy classifies epilepsy by the seizure type. Thus, epilepsy may be **focal**, **generalized**, or **combined generalized and focal**. The EEG may be helpful in facilitating classification.

C. Epilepsy Syndromes

Epilepsy syndromes are defined by constellations of seizure types, EEG findings, and imaging features, and often also depend on age at onset and comorbidities. Not every patient with epilepsy can be given a syndromic diagnosis. Several well-known epilepsy syndromes exist but are beyond the scope of this chapter.

► Etiology of Epilepsy

In parallel to classifying the seizure type, epilepsy type, and epilepsy syndrome (if applicable), the cause of the patient's seizures should be sought. The International League Against Epilepsy lists six broad etiologic categories; sometimes a patient's seizures have more than one etiology.

A. Structural Etiology

1. Pediatric age groups—Congenital abnormalities and perinatal injuries may result in seizures presenting in infancy or childhood.

2. Mesial temporal sclerosis—Hippocampal sclerosis is a recognized cause of focal and secondarily generalized seizures of uncertain etiology.

3. Trauma—Trauma is an important cause of seizures at any age, but especially in young adults. Posttraumatic epilepsy is more likely to develop if the dura mater was penetrated and generally becomes manifest within 2 years following the injury. Seizures developing in the first week after head injury do not necessarily imply that future attacks will occur. There is *no* evidence that prophylactic anticonvulsant medication treatment reduces the incidence of posttraumatic epilepsy.

4. Tumors and other space-occupying lesions—Neoplasms may lead to seizures at any age, but they are an especially important cause of seizures in middle and later life, when the incidence of neoplastic disease increases. Seizures are commonly the initial symptoms of the tumor and often are focal in character. They are most likely to occur with structural lesions involving the frontal, parietal, or temporal regions. *Tumors must be excluded by imaging studies (MRI preferred over CT) in all patients with onset of seizures after 20 years of age, focal seizures or signs, or a progressive seizure disorder.*

5. Vascular diseases—Stroke and other vascular diseases become increasingly frequent causes of seizures with advancing age and are the most common cause of seizures with onset at age 60 years or older.

6. Degenerative disorders—Alzheimer disease and other degenerative disorders are a cause of seizures in later life.

B. Genetic Etiology

This category encompasses a broad range of disorders, for which the age at onset ranges from the neonatal period to adolescence or even later in life. Monogenic disorders tend to exhibit an autosomal dominant pattern of inheritance, and where the mutation is known, the responsible gene often encodes a neuronal ion channel. A genetic etiology may also underpin certain epilepsies with a metabolic or structural basis.

C. Infectious Etiology

Infectious diseases must be considered in all age groups as potentially reversible causes of seizures. Seizures may occur with an acute infective or inflammatory illness, such as bacterial meningitis or herpes encephalitis, or in patients with more longstanding or chronic disorders, such as neurosyphilis or cerebral cysticercosis. In patients with AIDS, seizures may result from central nervous system toxoplasmosis, cryptococcal meningitis, secondary viral encephalitis, or other infective complications. Seizures are a common sequela of supratentorial brain abscess, developing most frequently in the first year after treatment.

D. Metabolic Etiology

Inborn errors of metabolism and other inherited conditions may cause epilepsy as one of their manifestations (eg, pyridoxine deficiency, mitochondrial disease); these disorders typically present during childhood.

E. Immune Etiology

Autoimmune diseases such as systemic lupus erythematosus and autoimmune limbic encephalitis may cause epilepsy; often the epilepsy can be cured with immunotherapy and lifelong antiepileptic medication treatment is not necessary.

F. Unknown Etiology

In many cases, the cause of epilepsy cannot be determined.

► Clinical Findings

A. Symptoms and Signs

Nonspecific changes such as headache, mood alterations, lethargy, and myoclonic jerking alert some patients to an impending seizure hours before it occurs. These **prodromal symptoms** are distinct from the **aura**; the aura that may precede a generalized seizure by a few seconds or minutes is itself a part of the seizure indicating focal onset from a restricted part of the brain.

In most patients, seizures occur unpredictably at any time and without any relationship to posture or ongoing activities. Occasionally, however, they occur at a particular time (eg, during sleep) or in relation to external precipitants such as lack of sleep, missed meals, emotional stress, menstruation, alcohol ingestion (or alcohol withdrawal), or use of certain recreational drugs. Fever and nonspecific infections may also precipitate seizures in patients with epilepsy. In a few patients, seizures are provoked by specific stimuli such as flashing lights or a flickering television set (**photosensitive epilepsy**), music, or reading.

Clinical examination between seizures shows no abnormality in patients with idiopathic epilepsy, but in the immediate postictal period, extensor plantar responses may be seen. The presence of lateralized or focal signs postictally suggests that seizures may have a focal origin. In patients with symptomatic epilepsy, the findings on examination will reflect the underlying cause.

B. Imaging

MRI is indicated for patients with focal neurologic symptoms or signs, focal seizures, or electroencephalographic findings of a focal disturbance. It should also be performed in patients with clinical evidence of a progressive disorder and in those with new onset of seizures after the age of 20 years because of the possibility of an underlying neoplasm. CT is generally less sensitive than MRI in detecting small structural brain abnormalities but may be used when MRI is contraindicated or unavailable.

C. Laboratory Studies

Initial investigations after a first seizure should include complete blood count, serum glucose, electrolytes, creatinine, calcium, magnesium, and liver biochemical tests to exclude various causes of provoked seizures and to provide a baseline for subsequent monitoring of long-term effects of treatment. Routine laboratory investigations are *not* usually necessary after recurrent seizures in patients with known epilepsy. A lumbar puncture may be necessary when any sign of infection is present or in the evaluation of new-onset seizures in the acute setting.

D. Electroencephalography

Electroencephalography may support the clinical diagnosis of epilepsy (by demonstrating paroxysmal abnormalities containing spikes or sharp waves), provide a guide to prognosis, and help classify the seizure disorder. Classification of the disorder is important for determining the most appropriate anticonvulsant medication with which to start treatment. For example, absence and focal seizures with impaired awareness may be difficult to distinguish clinically, but the electroencephalographic findings and treatment of choice differ in these two conditions. Finally, by localizing the epileptogenic source, the electroencephalographic findings are important in evaluating candidates for surgical treatment.

► Differential Diagnosis

The distinction between the various disorders likely to be confused with generalized seizures is usually made on the basis of the history. The importance of obtaining an eyewitness account of the attacks cannot be overemphasized.

A. Differential Diagnosis of Focal Seizures

1. TIA—These are distinguished from seizures by their longer duration, lack of spread, and negative (eg, weakness or numbness) rather than positive (eg, convulsive jerking or paresthesias) symptoms. Level of consciousness, which is unaltered, does not distinguish them.

2. Migraine aura—Migraine aura may produce positive or negative symptoms, tends to spread slowly from one part of the body to another (over minutes rather than seconds), and is usually longer in duration (minutes to hours). It is usually, but not always, followed by a typical migraine headache.

3. Panic attacks—These may be hard to distinguish from focal seizures unless there is evidence of an anxiety disorder between attacks and the attacks have a clear relationship to external circumstances.

4. Rage attacks—These are situational and lead to goal-directed aggressive behavior.

B. Differential Diagnosis of Generalized Seizures

1. Syncope—Syncopal episodes usually occur in relation to postural change, emotional stress, instrumentation, pain, or straining. They are typically preceded by pallor, sweating, nausea, and malaise and lead to loss of consciousness accompanied by flaccidity; recovery occurs rapidly with recumbency, and there is no postictal headache or confusion. In some instances, however, motor accompaniments and urinary incontinence may simulate a seizure.

2. Cardiac disease—Cerebral hypoperfusion due to a disturbance of cardiac rhythm should be suspected in patients with known cardiac or vascular disease or in elderly patients who present with episodic loss of consciousness. Prodromal symptoms are typically absent. Cardiac rhythm monitoring may be necessary to establish the diagnosis; external event recorders or implantable loop recorders may be valuable if the disturbances of consciousness are rare. A relationship of attacks to physical activity and the finding of a systolic murmur are suggestive of aortic stenosis.

3. Brainstem ischemia—Loss of consciousness is preceded or accompanied by other brainstem signs. Basilar artery migraine and vertebrobasilar vascular disease are discussed elsewhere in this chapter.

4. Psychogenic nonepileptic seizure (PNES)—Simulating an epileptic seizure, a PNES may occur due to a conversion disorder or malingering. Many patients also have epileptic seizures or a family history of epilepsy. A history of childhood physical or sexual abuse is common. Although a PNES tends to occur at times of emotional stress, this may also be the case with epileptic seizures.

Clinically, the attacks superficially resemble tonic-clonic seizures, but there may be obvious preparation before a PNES. Moreover, there is usually no tonic phase; instead, there may be an asynchronous thrashing of the limbs and the attack rarely leads to injury. Eyes are often forcibly closed during PNES, unlike epileptic seizures, in which they are typically open. Consciousness may be normal or “lost,” but in the latter context the occurrence of goal-directed behavior or of shouting, swearing, etc, indicates that it is feigned. Postictally, there are no changes in behavior or neurologic findings.

Often, clinical observation is insufficient to discriminate epileptic from nonepileptic seizures and **video electroencephalographic monitoring** is required. Elevation of serum prolactin level to at least twice the upper limit of normal can be seen between 10 and 20 minutes after a seizure or syncopal event but not after a PNES. However, prolactin measurement has limited clinical utility because levels are normal after an epileptic seizure in roughly half of patients and a baseline prolactin must be drawn 6 hours after the attack.

Treatment

A. General Measures

For patients with epilepsy, medication is prescribed with the goal of preventing further attacks and is usually continued until there have been no seizures for at least 2 years. Patients should be advised to avoid situations that could be dangerous or life-threatening if further seizures should occur. Legislation may require clinicians to report to the state authorities any patients with seizures or other episodic disturbances of consciousness; *driving cessation for 6 months* or as legislated is appropriate following an unprovoked seizure.

1. Choice of medication—Medication selection depends on seizure type (Table 24–2). The dose of the selected anticonvulsant is gradually increased until seizures are controlled or side effects prevent further increases. If seizures continue despite treatment at the maximal tolerated dose, a second medication is added and the dose increased depending on tolerance; the first medication is then gradually withdrawn. In most patients with seizures of a single type, satisfactory control can be achieved with a single anticonvulsant. Treatment with two medications may further reduce seizure frequency or severity but usually only at the cost of greater toxicity. Treatment with more than two medications is almost always unhelpful unless the patient is having seizures of different types. Other factors to consider in selecting an anticonvulsant include likely side effects, teratogenicity, interactions with other medications and oral contraceptives, and route of metabolism.

All antiepileptics are potentially teratogenic, although the teratogenicity of the newer antiseizure medications is less clear. Nevertheless, antiepileptic medication must be given to pregnant women with epilepsy to prevent seizures, which can pose serious risk to the fetus from trauma, hypoxia, or other factors.

2. Monitoring—Individual differences in drug metabolism cause a given dose of a medication to produce different

blood concentrations in different patients, and this will affect the therapeutic response. In general, *the dose of an antiepileptic agent is increased, depending on tolerance, to achieve the desired clinical response regardless of the serum drug level*. When a dose is reached that either controls seizures or is the maximum tolerated, then a steady-state trough drug level may be obtained for future reference; rechecking this level may be appropriate during pregnancy, if a breakthrough seizure occurs, a dose change occurs, or another (potentially interacting) medication is added to the regimen. A laboratory's therapeutic range for a medication is only a guide; many patients achieve good seizure control with no adverse effect at serum levels that exceed the stipulated range, and in these cases no dose adjustment is needed. The most common cause of a lower concentration of medication than expected for the prescribed dose is suboptimal patient adherence. Adherence can be improved by limiting to a minimum the number of daily doses. Recurrent seizures or status epilepticus may result if medications are taken erratically, and in some circumstances nonadherent patients may be better off without any medication. All anticonvulsants have side effects, and many require baseline and regular laboratory monitoring (Table 24–2).

3. Discontinuance of medication—Only when adult patients have been seizure-free for 2 years should withdrawal of medication be considered. Unfortunately, there is no way of predicting which patients can be managed successfully without treatment, although seizure recurrence is more likely in (1) patients with a longer duration of epilepsy prior to remission, (2) those with a shorter duration of remission, (3) those who initially did not respond to therapy, (4) those with seizures having focal features or of multiple types, (5) those with onset during adulthood, and (6) those with continuing electroencephalographic abnormalities. Dose reduction should be gradual (over weeks or months), and medications should be withdrawn one at a time. If seizures recur, treatment is reinstated with the previously effective regimen.

4. Surgical treatment—Patients with seizures refractory to two or more medications may be candidates for operative treatment. Surgical resection is most efficacious when there is a single well-defined seizure focus, particularly in the temporal lobe. Among well-chosen patients, up to 70% remain seizure-free after extended follow-up. Additional surgical techniques for medically refractory epilepsy approved in the United States include laser interstitial thermal therapy, deep brain stimulation, responsive cortical stimulation, and vagus nerve stimulation.

B. Special Circumstances

1. Solitary seizures—In patients who have had only one seizure or a flurry of seizures over a brief period of several hours, investigation as outlined earlier should exclude an underlying cause requiring specific treatment. An electroencephalogram should be obtained, preferably within 24 hours after the seizure. Prophylactic anticonvulsant treatment is generally not required unless further attacks occur or investigations reveal underlying pathology. The risk of seizure recurrence varies in different series between about

30% and 70%, with higher risk of recurrence in patients with structural brain lesions or abnormalities on electroencephalogram. Epilepsy should *not* be diagnosed on the basis of a solitary seizure. If seizures occur in the context of transient, nonrecurrent systemic disorders such as hyponatremia or hypoglycemia, the diagnosis of epilepsy is inaccurate, and long-term prophylactic anticonvulsant treatment is unnecessary.

2. Alcohol withdrawal seizures—The characteristic alcohol withdrawal seizure pattern is one or more generalized tonic-clonic seizures that may occur within 48 hours or so of withdrawal from alcohol after a period of high or prolonged intake. If the seizures have consistently focal features, the possibility of an associated structural abnormality, often traumatic in origin, must be considered. Treatment with anticonvulsants is generally not required for alcohol withdrawal seizures, since they are self-limited. Benzodiazepines are effective and safe for preventing further seizures. Status epilepticus may complicate alcohol withdrawal and is managed along conventional lines. Further attacks will not occur if the patient abstains from alcohol.

3. Tonic-clonic status epilepticus—Poor adherence to the anticonvulsant regimen is the most common cause; however, any disorder that can cause a single seizure may be responsible. The mortality rate may be as high as 20%, and among survivors the incidence of neurologic and cognitive sequelae is high. The prognosis relates to the underlying cause as well as the length of time between onset of status epilepticus and the start of effective treatment.

Status epilepticus is a medical emergency. Initial management includes maintenance of the airway and 50% dextrose (25–50 mL) intravenously in case hypoglycemia is responsible. If seizures continue, an intravenous bolus of lorazepam, 4 mg, is given at a rate of 2 mg/min and repeated once after 10 minutes if necessary; alternatively, 10 mg of midazolam is given intramuscularly, and again after 10 minutes if necessary. Diazepam can also be given rectally as a gel (0.2 mg/kg). These measures are usually effective in halting seizures for a brief period. Respiratory depression and hypotension may complicate the treatment and are treated as in other circumstances, including intubation and mechanical ventilation and admission to an intensive care unit.

Regardless of the response to lorazepam or midazolam, fosphenytoin or phenytoin should be administered intravenously. Fosphenytoin (18–20 mg phenytoin equivalents [PE]/kg) is rapidly and completely converted to phenytoin following intravenous administration and is preferred because it is less likely to cause reactions at the infusion site, can be given with all common intravenous solutions, and may be administered at a faster rate (150 mg PE/min). When fosphenytoin is not available, phenytoin (18–20 mg/kg) is given intravenously at a rate of 50 mg/min. Phenytoin is best injected directly but can also be given in saline; it precipitates, however, if injected into glucose-containing solutions. Because arrhythmias may develop during rapid administration of fosphenytoin or phenytoin, electrocardiographic monitoring is prudent. Hypotension may occur, especially if diazepam has also been given. Alternatively or

additionally, intravenous valproate (loading dose 20–40 mg/kg over 15 min, maximum dose 3000 mg) or levetiracetam (loading dose 60 mg/kg over 15 min, maximum dose 4500 mg) is used for status epilepticus. Although neither is approved by the FDA for this indication, both were equivalent to fosphenytoin in a randomized trial. Due to the teratogenicity of valproate, it should be avoided in women who may be pregnant.

If seizures continue, phenobarbital is then given in a loading dose of 10–20 mg/kg intravenously by slow or intermittent injection (50 mg/min). Respiratory depression and hypotension are especially common with this therapy.

If these measures fail, general anesthesia with ventilatory assistance may be required; some experts recommend proceeding directly to general anesthesia if convulsions do not cease after the initial 18–20 PE/kg fosphenytoin load. Intravenous midazolam may provide control of refractory status epilepticus; the suggested loading dose is 0.2 mg/kg, followed by 0.05–0.2 mg/kg/h. Propofol (1–2 mg/kg as an intravenous bolus, followed by infusion at 2–15 mg/kg/h depending on response) may also be used, as may pentobarbital (5–15 mg/kg intravenously, followed by 0.5–4 mg/kg/h).

After status epilepticus is controlled, an oral medication program for the long-term management of seizures is started, and investigations into the cause of the disorder are pursued.

4. Nonconvulsive status epilepticus—In some cases, status epilepticus presents not with convulsions, but with a fluctuating abnormal mental status, confusion, impaired responsiveness, and automatism. Electroencephalography establishes the diagnosis. The treatment approach outlined above applies to any type of status epilepticus, although intravenous anesthesia is usually not necessary. The prognosis is a reflection of the underlying cause rather than of continuing seizures.

► When to Refer

- Behavioral episodes of uncertain nature.
- Seizures are difficult to control with monotherapy.
- There is a progressive neurologic disorder.

► When to Admit

- Status epilepticus.
- Frequent seizures requiring rapid medication titration and electroencephalographic monitoring.
- For inpatient monitoring when PNES is suspected.

Ahmad S et al. Surgical treatments of epilepsy. *Semin Neurol.* 2020;40:696. [PMID: 33176368]

Kanner AM et al. Practice guideline update summary: efficacy and tolerability of the new antiepileptic drugs I: treatment of new-onset epilepsy. *Epilepsy Curr.* 2018;18:260. [PMID: 30254527]

Kapur J et al; NETT and PECARN Investigators. Randomized trial of three anticonvulsant medications for status epilepticus. *N Engl J Med.* 2019;381:2103. [PMID: 31774955]

DYSAUTONOMIA



ESSENTIALS OF DIAGNOSIS

- ▶ Postural hypotension or abnormal heart rate regulation.
- ▶ Abnormalities of sweating, intestinal motility, sexual function, or sphincter control.
- ▶ Syncope may occur.
- ▶ Symptoms occur in isolation or any combination.

► General Considerations

Dysautonomia may occur as a result of pathological processes in the central or peripheral nervous system. It is manifested by a variety of symptoms related to abnormalities of blood pressure regulation, thermoregulatory sweating, gastrointestinal function, sphincter control, sexual function, respiration, and ocular function. The differential diagnosis depends on the time course of autonomic dysfunction and whether dysautonomia is an isolated symptom or associated with central or peripheral neurologic symptoms and signs.

A. Causes in the Central Nervous System

Disease at certain sites, regardless of its nature, may lead to dysautonomic symptoms. **Postural hypotension**, which is usually the most troublesome and disabling symptom, may result from spinal cord transection and other myelopathies (eg, due to tumor or syringomyelia) above the T6 level or from brainstem lesions such as syringobulbia and posterior fossa tumors. **Sphincter or sexual disturbances** may result from cord lesions at any level. Certain primary degenerative disorders are responsible for dysautonomia occurring in isolation (**pure autonomic failure**) or in association with more widespread abnormalities (**multisystem atrophy**) that may include parkinsonism, pyramidal symptoms, and cerebellar deficits. Postural hypotension is also a prominent symptom of idiopathic Parkinson disease and dementia with Lewy bodies.

B. Causes in the Peripheral Nervous System

A pure autonomic neuropathy may occur acutely or subacutely after a viral infection or as a paraneoplastic disorder related usually to small cell lung cancer, particularly in association with certain antibodies, such as anti-Hu or those directed at neuronal nicotinic ganglionic acetylcholine receptors. Dysautonomia is often conspicuous in patients with Guillain-Barré syndrome, manifesting with marked hypotension or hypertension or cardiac arrhythmias that may have a fatal outcome. It may also occur with diabetic, uremic, amyloidotic, and various other metabolic or toxic neuropathies; in association with leprosy or Chagas disease; and as a feature of certain hereditary neuropathies with autosomal dominant or recessive inheritance or an X-linked pattern. Autonomic symptoms are prominent

in the crises of hepatic porphyria. Small fiber neuropathies may underlie some cases of **postural orthostatic tachycardia syndrome (POTS)** due to impaired contractility in denervated venules and resulting preload failure (see below). Patients with botulism or the Lambert-Eaton myasthenic syndrome may have constipation, urinary retention, and a sicca syndrome as a result of impaired cholinergic function.

► Clinical Findings

A. Symptoms and Signs

Dysautonomic symptoms include syncope, postural hypotension, paroxysmal hypertension, persistent tachycardia without other cause, facial flushing, hypohidrosis or hyperhidrosis, vomiting, constipation, diarrhea, dysphagia, abdominal distention, disturbances of micturition or defecation, erectile dysfunction, apneic episodes, and declining night vision. In syncope, prodromal malaise, nausea, headache, diaphoresis, pallor, visual disturbance, loss of postural tone, and a sense of weakness and impending loss of consciousness are followed by actual loss of consciousness. It is usually accompanied by hypotension and bradycardia and may occur in response to emotional stress, postural hypotension, vigorous exercise in a hot environment, obstructed venous return to the heart, acute pain or its anticipation, fluid loss, and a variety of other circumstances. Although the patient is usually flaccid, some motor activity is not uncommon, and urinary (and rarely fecal) incontinence may also occur, thereby simulating a seizure. Recovery is rapid once the patient becomes recumbent, but headache, nausea, and fatigue commonly persist.

B. Evaluation of the Patient

The extent and severity of autonomic dysfunction should be determined, and the presence of associated neurologic symptoms and signs ascertained. Bedside testing of autonomic function includes examination of pupillary reactivity, examination of the skin for areas of excessive or reduced sweating and of the hands and feet for color or temperature changes, as well as assessment of blood pressure and heart rate in the supine position and 2 minutes after standing. With dysautonomia, *postural hypotension is not accompanied by a compensatory rise in heart rate*. Specialized tests include the cardiovascular response to the Valsalva maneuver and deep respiration, tilt-table testing, the thermoregulatory sweat test, the quantitative sudomotor axon reflex test, and the quantitative direct and indirect axon reflex test. Tests of gastrointestinal motility and urodynamics may be helpful when symptoms of dysmotility, incontinence, or urinary retention are present.

The neurologic examination should focus on detecting signs of parkinsonism, cerebellar dysfunction, disorders of neuromuscular transmission, and peripheral neuropathy. All patients should be tested for vitamin B₁₂ deficiency and diabetes. Patients with acute or subacute isolated dysautonomia should undergo testing for ganglionic acetylcholine receptor, anti-Hu, voltage-gated potassium channel complex, and voltage-gated calcium channel antibodies. For those with evidence of peripheral neuropathy, nerve

conduction studies; electromyography; and testing for HIV, amyloidosis, Sjögren syndrome, and Fabry disease are indicated. If there is evidence of central pathology, imaging studies will exclude a treatable structural cause. If the neurologic examination is normal, reversible, nonneurologic causes of symptoms must be considered. Isolated postural hypotension and syncope may relate to a reduced cardiac output, paroxysmal cardiac dysrhythmias, volume depletion, various medications, and endocrine and metabolic disorders such as Addison disease, hypothyroidism or hyperthyroidism, pheochromocytoma, and carcinoid syndrome.

► Treatment

The most disabling symptoms are usually postural hypotension and syncope. Abrupt postural change, prolonged recumbency, heavy meals, and other precipitants should be avoided. Medications associated with postural hypotension should be discontinued or reduced in dose. Treatment may include wearing waist-high elastic hosiery, salt supplementation, sleeping in a semierect position (which minimizes the natriuresis and diuresis that occur during recumbency), ingestion of 500 mL water 30 minutes before arising, and fludrocortisone (0.1–0.5 mg orally daily). Vasoconstrictor agents may be helpful and include midodrine (2.5–10 mg orally three times daily), droxidopa (100–600 mg orally three times daily), and ephedrine (15–30 mg orally three times daily). Other agents that have been used occasionally or experimentally are dihydroergotamine, yohimbine, pyridostigmine, and clonidine; refractory cases may respond to erythropoietin (epoetin alfa) or desmopressin. Patients must be monitored for recumbent hypertension. Postprandial hypotension is helped by caffeine. There is no satisfactory treatment for disturbances of sweating, but an air-conditioned environment is helpful in avoiding extreme swings in body temperature.

► When to Refer

- When the diagnosis is uncertain.
- When symptoms persist despite conventional treatment.

Shibao CA et al. Management of orthostatic hypotension, postprandial hypotension, and supine hypertension. *Semin Neurol*. 2020;40:515. [PMID: 33058087]

POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME

► Clinical Findings

In POTS, orthostatic symptoms (tremulousness, lightheadedness, palpitations, visual disturbances, weakness, fatigue, anxiety, hyperventilation, nausea) develop with a significant tachycardia (an increase of 30 beats/min or more or a heart rate of 120 beats/min or more) within 10 minutes of standing, in the absence of postural hypotension or an autonomic neuropathy. POTS is more common in women than men

and in patients between 20 and 50 years of age. Other medical problems causing a tachycardia must be excluded.

Its pathophysiology is uncertain but may involve cardiac deconditioning; impaired peripheral vasoconstriction due to peripheral sympathetic denervation, leading to venous pooling in the legs on standing and a compensatory tachycardia ("neuropathic POTS"); or an exaggerated sympathetic response to standing, with markedly elevated levels of plasma norepinephrine causing the tachycardia ("hyperadrenergic POTS"). Other possible mechanisms include hypovolemia, possibly from impaired function of the renin-angiotensin system ("volume dysregulation POTS") and excessive mast cell activation leading to inappropriate release of histamine during physical activity. Psychological mechanisms have also been invoked. POTS may be associated with joint hypermobility syndrome and mitral valve prolapse, and it may follow pregnancy, surgery, trauma, chemotherapy, vaccinations, or viral infections.

► Treatment

Management may involve volume repletion, a high salt diet and copious fluids, postural and psychophysiologic training, and a graduated exercise program. Medication treatment may include a beta-blocking agent (eg, propranolol 10–40 mg three times daily), phenobarbital (15 mg in the morning, 60 mg at night) or clonidine (0.2 mg twice daily) for patients with hyperadrenergic POTS; and midodrine (2.5–10 mg three times daily) or fludrocortisone (0.1–0.2 mg daily) if the blood pressure is low. The long-term prognosis is unclear but approximately 50% of patients recover within 3 years.

TRANSIENT ISCHEMIC ATTACKS



ESSENTIALS OF DIAGNOSIS

- Focal neurologic deficit of acute onset.
- Clinical deficit resolves completely within 24 hours.
- Risk factors for vascular disease often present.

► General Considerations

Transient ischemic attacks (TIAs) are characterized by *focal ischemic cerebral neurologic deficits that last for less than 24 hours* (usually less than 1–2 hours). About 30% of patients with stroke have a history of TIAs and 5–10% of patients with TIAs will have a stroke within 90 days. The natural history of attacks is variable. Some patients will have a major stroke after only a few attacks, whereas others may have frequent attacks for weeks or months without having a stroke. The risk of stroke is high in the first 3 months after an attack, particularly in the first month and especially within the first 48 hours. The stroke risk is greater in patients older than 60 years, in patients with diabetes, or after TIAs that last longer than 10 minutes and with symptoms or signs

of weakness, speech impairment, or gait disturbance. In general, carotid ischemic attacks are more liable than vertebrobasilar ischemic attacks to be followed by stroke.

Urgent intervention in TIA patients reduces rates of subsequent stroke, and *the condition should be treated with a similar sense of urgency as unstable angina*.

► Etiology

An important cause of transient cerebral ischemia is embolization. In many patients with these attacks, a source is readily apparent in the heart or a major extracranial artery to the head, and emboli sometimes are visible in the retinal arteries. An embolic phenomenon explains why separate attacks may affect different parts of the territory supplied by the same major vessel. Cardiac causes of embolic ischemic attacks include atrial fibrillation, heart failure, infective and nonbacterial thrombotic endocarditis, atrial myxoma, and mural thrombi complicating myocardial infarction. Atrial septal defects and patent foramen ovale may permit venous thromboemboli to reach the brain (**paradoxical emboli**). An ulcerated plaque on a major artery to the brain may serve as a source of emboli. In the anterior circulation, atherosclerotic changes occur most commonly in the region of the carotid bifurcation extracranially; these changes may cause a bruit. Atherosclerosis also affects the vertebrobasilar system and the major intracranial vessels including the middle and anterior cerebral arteries.

Less common abnormalities of blood vessels that may cause TIAs include fibromuscular dysplasia, which affects particularly the cervical internal carotid artery; atherosclerosis of the aortic arch; inflammatory arterial disorders such as giant cell arteritis, polyarteritis, and granulomatous angiitis; and meningovascular syphilis. Critical stenosis of a major extracranial or intracranial artery may cause TIA, especially in the setting of hypotension.

Hematologic causes of TIA include polycythemia, sickle cell disease, hyperviscosity syndromes, and the antiphospholipid antibody syndrome. Severe anemia may also lead to transient focal neurologic deficits in patients with preexisting cerebral arterial disease.

The **subclavian steal syndrome** may lead to transient vertebrobasilar ischemia. Symptoms develop when there is localized stenosis or occlusion of one subclavian artery proximal to the source of the vertebral artery, so that blood is “stolen” from the vertebral artery to supply the arm. A bruit in the supraclavicular fossa, unequal radial pulses, and a difference of 20 mm Hg or more between the systolic blood pressures in the arms should suggest the diagnosis in patients with vertebrobasilar TIAs.

► Clinical Findings

A. Symptoms and Signs

The symptoms of TIAs vary markedly among patients; however, the symptoms in a given individual tend to be constant in type. Onset is abrupt and without warning, and recovery usually occurs rapidly, often within a few minutes. The specific symptoms depend on the arterial distribution affected,

as outlined in the subsequent section on stroke. Of note, TIA rarely causes loss of consciousness or acute confusion but is often erroneously blamed for such symptoms.

B. Imaging

CT or MRI scan is indicated within 24 hours of symptom onset, in part to exclude the possibility of a small cerebral hemorrhage or a cerebral tumor masquerading as a TIA. MRI with diffusion-weighted sequences is particularly sensitive for revealing acute or subacute infarction, which is seen in up to one-third of cases despite resolution of clinical symptoms and indicates a high risk of subsequent stroke. Noninvasive imaging of the cervical vasculature should also be performed; carotid duplex ultrasonography is useful for detecting significant stenosis of the internal carotid artery, and MR or CT angiography permits broader visualization of cervical and intracranial vasculature.

C. Laboratory and Other Studies

Clinical and laboratory evaluation must include assessment for hypertension, heart disease, hematologic disorders, diabetes mellitus, hyperlipidemia, and peripheral vascular disease. It should include complete blood count, fasting blood glucose and serum cholesterol determinations, and may include serologic tests for syphilis and HIV infection. An ECG should be obtained. Echocardiography with agitated saline contrast is performed if a cardioembolic source is likely, and blood cultures are obtained if endocarditis is suspected. Ambulatory ECG monitoring is indicated to detect paroxysmal atrial fibrillation and, if the cause of the TIA remains elusive, *extended monitoring* may detect paroxysmal atrial fibrillation in up to 20% of patients.

► Differential Diagnosis

Focal seizures usually cause abnormal motor or sensory phenomena such as clonic limb movements, paresthesias, or tingling, rather than weakness or loss of feeling. Symptoms generally spread (“march”) up the limb and may lead to a generalized tonic-clonic seizure.

Classic migraine is easily recognized by the visual premonitory symptoms, followed by nausea, headache, and photophobia, but less typical cases may be hard to distinguish. Patients with migraine are typically younger, commonly have a history of episodes since adolescence, and report that other family members have a similar disorder.

Focal neurologic deficits may occur during periods of hypoglycemia in diabetic patients receiving insulin or oral hypoglycemic agent therapy.

► Treatment

A. Medical Measures

Medical treatment is aimed at preventing further attacks and stroke. Treat diabetes mellitus, hematologic disorders, and hypertension, preferably with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. A

statin should be started regardless of the current low-density lipoprotein level (LDL), although this practice is only supported by randomized trial data in patients with an LDL greater than 100 mg/dL. Cigarette smoking should be stopped, and cardiac sources of embolization should be treated appropriately. Weight reduction and regular physical activity should be encouraged when appropriate. An antiplatelet or anticoagulant should be started as soon as imaging has established the absence of hemorrhage.

1. Hospitalization—Hospitalization should be considered for patients seen within a week of the attack, when they are at increased risk for early recurrence. One commonly used method to assess recurrence risk is the **ABCD² score**; points are assigned for each of the following criteria: age 60 years or older (1 point), blood pressure 140/90 mm Hg or higher (1 point), clinical symptoms of focal weakness (2 points) or speech impairment without weakness (1 point), duration of 60 minutes or longer (2 points) or 10–59 minutes (1 point), or diabetes mellitus (1 point). An ABCD² score of 4 or more points has been suggested as a threshold for hospital admission. The **ABCD^{2I}** (with an additional 3 points for any abnormal diffusion-weighted MRI finding or any infarct [new or old] on noncontrast CT) has been proposed as a better predictor of subsequent stroke risk. Admission is also advisable for patients with crescendo attacks, symptomatic carotid stenosis, or a known cardiac source of emboli or hypercoagulable state; such hospitalization facilitates early intervention for any recurrence and rapid institution of secondary prevention measures.

2. Anticoagulation—The chief indication for anticoagulation after TIA is atrial fibrillation. Patients with metal heart valves, left ventricular thrombus, and the antiphospholipid antibody syndrome should also receive anticoagulation therapy. Treatment is with warfarin (target INR 2.0–3.0); bridging warfarin with heparin is not necessary, but some experts advocate treatment with aspirin until the INR becomes therapeutic. For long-term anticoagulation in the setting of atrial fibrillation, apixaban (2.5–5 mg orally twice daily), dabigatran (150 mg orally twice daily), edoxaban (60 mg orally daily), and rivaroxaban (20 mg orally daily) are options. Combination antiplatelet-anticoagulation therapy is only indicated in patients with mechanical heart valves or those with a separate indication for antiplatelet therapy such as a cardiac stent. In patients with cardiomyopathy and an ejection fraction under 35% without atrial fibrillation, warfarin (target INR 2.0–3.0) reduces ischemic stroke risk compared to aspirin but results in a roughly equivalent increase in the risk of major hemorrhage; treatment in this population should therefore be individualized.

3. Antiplatelet therapy—All patients in whom anticoagulation is not indicated should be treated with short-term dual antiplatelet therapy and long-term monotherapy to reduce the frequency of TIAs and the incidence of stroke. Treatment should be initiated within 12 hours after the TIA or minor stroke (defined by a National Institutes of

Health Stroke Scale of 3 or less) with an oral loading dose of clopidogrel (300–600 mg) followed by 75 mg/day orally plus aspirin (50–325 mg daily orally) for 21 days, followed by monotherapy with aspirin (81 mg daily orally), aspirin combined with extended-release dipyridamole (200 mg twice daily orally), or clopidogrel (75 mg daily orally). Cilostazol (100 mg twice daily) had similar efficacy as aspirin at long-term stroke prevention in an Asian population with less risk of hemorrhage. Combining clopidogrel with aspirin beyond 90 days increases the risk of hemorrhagic complications and is *not* recommended.

B. Surgical or Endovascular Measures

1. Carotid revascularization—When arteriography reveals a surgically accessible high-grade stenosis (70–99% in luminal diameter) on the side appropriate to carotid ischemic attacks, operative treatment (**carotid endarterectomy**) or **endovascular intervention** reduces the risk of ipsilateral carotid stroke, especially when TIAs are of recent onset (less than 1 month) and when the perioperative morbidity and mortality risk is estimated to be less than 6%. Endovascular therapy carries a slightly higher procedural stroke risk than endarterectomy in patients older than 70 years and is generally reserved for younger patients whose neck anatomy is unfavorable for surgery. Patients with symptomatic carotid stenosis of 50–69% derive moderate benefit from intervention, but surgery is not indicated for mild stenosis (less than 50%).

2. Closure of patent foramen ovale—Carefully selected patients with patent foramen ovale (PFO) and right-to-left shunt benefit from PFO closure and antiplatelet therapy. Patients should be considered for PFO closure if they are between 18 and 60 years old; have had a cryptogenic stroke or TIA; and do not have uncontrolled diabetes, hypertension, or a specific indication for long-term anticoagulation. A cryptogenic stroke does not have an identified mechanism, such as large artery atherosclerosis (greater than or equal to 30–50% stenosis of the intracranial or cervical arteries or a plaque greater than or equal to 4mm thick in the aortic arch), known cardioembolic source (eg, atrial fibrillation), small vessel arteriolosclerosis (eg, lacunar stroke smaller than 1.5 cm in diameter), hypercoagulable state, or dissection. Patients with moderate to large interatrial shunts or associated atrial septal aneurysms appear to benefit most from PFO closure. See also Chapter 10.

► When to Refer

All patients should be referred for urgent investigation and *treatment to prevent stroke*.

► When to Admit

If seen within a week of a TIA, patients should be considered for admission when they have an ABCD² score of 4 points or more, when outpatient evaluation is impractical, or when there are multiple attacks, carotid stenosis of greater than 70%, or other concern for early recurrence or stroke.

Pan Y et al. Outcomes associated with clopidogrel-aspirin use in minor stroke or transient ischemic attack: a pooled analysis of Clopidogrel in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events (CHANCE) and Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trials. *JAMA Neurol.* 2019;76:1466. [PMID: 31424481]

STROKE



ESSENTIALS OF DIAGNOSIS

- ▶ Sudden onset of neurologic deficit of cerebrovascular origin.
- ▶ Patient often has hypertension, diabetes mellitus, tobacco use, atrial fibrillation, or atherosclerosis.
- ▶ Distinctive neurologic signs reflect the region of the brain involved.

► General Considerations

In the United States, stroke is the sixth leading cause of death and a leading cause of disability. Risk factors for stroke include hypertension, diabetes mellitus, hyperlipidemia, cigarette smoking, cardiac disease, HIV infection, trigeminal herpes zoster, recreational drug abuse, heavy alcohol consumption, and a family history of stroke.

Strokes are subdivided pathologically into **infarcts** and **hemorrhages**. The distinction may be difficult clinically; CT scanning is essential to clarify the pathologic basis (Table 24–3).

1. Lacunar Infarction

Lacunar infarcts are small lesions (usually less than 1.5 cm in diameter) that occur in the distribution of short penetrating arterioles in the basal ganglia, pons, cerebellum, internal capsule, thalamus, and, less commonly, the deep cerebral white matter (Table 24–3). Lacunar infarcts are associated with poorly controlled hypertension or diabetes and have been found in several clinical syndromes, including contralateral pure motor hemiparesis or pure hemisensory deficit, ipsilateral ataxia with hemiparesis, and dysarthria with clumsiness of the hand. The neurologic deficit may progress over 24–36 hours before stabilizing.

Early mortality and risk of stroke recurrence is higher for patients with nonlacunar than lacunar infarcts. The prognosis for recovery from the deficit produced by a lacunar infarct is usually good, with partial or complete resolution occurring over the following 4–6 weeks in many instances. Treatment is as described for TIA and cerebral infarction.

2. Cerebral Infarction

Thrombotic or embolic occlusion of a major vessel leads to cerebral infarction. Causes are identical to the disorders predisposing to TIAs. The resulting deficit depends on the particular vessel involved and the extent of any collateral

circulation. Cerebral ischemia leads to release of excitatory and other neuropeptides that may augment calcium flux into neurons, thereby leading to cell death and increasing the neurologic deficit.

► Clinical Findings

A. Symptoms and Signs

Onset is usually abrupt, and there may then be very little progression except that due to brain swelling. Clinical evaluation should always include examination of the heart for murmurs and rhythm irregularities. Auscultating over the carotid or subclavian vessels may reveal a bruit but is not sensitive enough to substitute for vascular imaging.

1. Obstruction of carotid circulation—Occlusion of the anterior cerebral artery distal to its junction with the anterior communicating artery causes weakness and cortical sensory loss in the contralateral leg and sometimes mild weakness of the arm, especially proximally. There may be a contralateral grasp reflex, paratonic rigidity, abulia (lack of initiative), or frank confusion. Urinary incontinence is not uncommon, particularly if behavioral disturbances are conspicuous. Bilateral anterior cerebral infarction is especially likely to cause marked behavioral changes and memory disturbances. Unilateral anterior cerebral artery occlusion proximal to the junction with the anterior communicating artery is generally well tolerated because of the collateral supply from the other side.

Middle cerebral artery occlusion leads to contralateral hemiplegia, hemisensory loss, and homonymous hemianopia (ie, bilaterally symmetric loss of vision in half of the visual fields), with the eyes deviated to the side of the lesion. If the dominant hemisphere is involved, global aphasia is also present. It may be impossible to distinguish this clinically from occlusion of the internal carotid artery. With occlusion of either of these arteries, there may also be considerable swelling of the hemisphere during the first 72 hours. For example, an infarct involving one cerebral hemisphere may lead to such swelling that the function of the other hemisphere or the rostral brainstem is disturbed and coma results. Occlusions of different branches of the middle cerebral artery cause more limited findings. For example, involvement of the superior division in the dominant hemisphere leads to a predominantly expressive (**Broca**) aphasia and to contralateral paralysis and loss of sensations in the arm, the face and, to a lesser extent, the leg. Inferior branch occlusion in the dominant hemisphere produces a receptive (**Wernicke**) aphasia and a homonymous visual field defect. With involvement of the non-dominant hemisphere, speech and comprehension are preserved, but there may be a left hemispatial neglect syndrome or constructional and visuospatial deficits.

Occlusion of the **ophthalmic or central retinal artery** leads to sudden painless visual loss with retinal pallor and a macular cherry red spot on fundoscopic examination. Sudden, transient vision loss in one eye (**amaurosis fugax**) is a TIA in this arterial territory. Patients with a **cilioretinal artery** (approximately 25%) may have macular sparing due to collateral blood supply.

Table 24–3. Features of the major stroke subtypes.

Stroke Type and Subtype	Clinical Features	Diagnosis	Treatment
Ischemic Stroke			
Lacunar infarct	Small (< 1.5 cm) lesions in the basal ganglia, pons, cerebellum, or internal capsule; less often in deep cerebral white matter; prognosis generally good; clinical features depend on location, but may worsen over first 24–36 hours.	MRI with diffusion-weighted sequences usually defines the area of infarction; CT is insensitive acutely but can be used to exclude hemorrhage.	Antiplatelet; control risk factors (hypertension, tobacco use, hypercholesterolemia, and diabetes mellitus).
Carotid circulation obstruction	See text—signs vary depending on occluded vessel.	Noncontrast CT to exclude hemorrhage but findings may be normal during first 6–24 hours of an ischemic stroke; diffusion-weighted MRI is gold standard for identifying acute stroke; electrocardiography, carotid duplex studies, echocardiography, blood glucose, complete blood count, and tests for hyperlipidemia are indicated; ambulatory ECG monitoring, including extended monitoring in selected instances; CTA, MRA, or conventional angiography in selected cases; tests for hypercoagulable states in selected cases.	0–3 hours in United States: intravenous thrombolytics (approved in Europe for up to 4.5 hours). 0–6 hours: endovascular mechanical embolectomy. 6–24 hours: endovascular mechanical embolectomy in select cases. Secondary prevention: antiplatelet agent is first-line therapy; anticoagulation without heparin bridge for cardioembolic strokes due to atrial fibrillation and other select cases when no contraindications exist; control risk factors as above.
Vertebralbasilar occlusion	See text—signs vary based on location of occluded vessel.	As for carotid circulation obstruction.	As for carotid circulation obstruction.
Hemorrhagic Stroke			
Spontaneous intracerebral hemorrhage	Commonly associated with hypertension; also with bleeding disorders, amyloid angiopathy. Hypertensive hemorrhage is located commonly in the basal ganglia, pons, thalamus, cerebellum, and less commonly the cerebral white matter.	Noncontrast CT is superior to MRI for detecting bleeds of < 48 hours duration; laboratory tests to identify bleeding disorder: angiography may be indicated to exclude aneurysm or AVM in younger patients without hypertension. Do not perform lumbar puncture.	Lower systolic blood pressure to 140 mm Hg; cerebellar bleeds or hematomas with gross mass effect may require urgent surgical evacuation. AVM: surgical resection indicated to prevent further bleeding; other modalities to treat nonoperable AVMs available at specialized centers.
Subarachnoid hemorrhage	Present with sudden onset of worst headache of life, may lead rapidly to loss of consciousness; signs of meningeal irritation often present; etiology usually aneurysm or AVM, but 20% have no source identified.	CT to confirm diagnosis, but may be normal in rare instances; if CT negative and suspicion high, perform lumbar puncture to look for red blood cells or xanthochromia; angiography to determine source of bleed in candidates for treatment.	Lower systolic blood pressure to < 140 mm Hg immediately. Aneurysm: prevent further bleeding by clipping aneurysm or coil embolization; nimodipine helps prevent vasospasm; once aneurysm has been obliterated intravenous fluids and induced hypertension to prevent vasospasm; angioplasty may also reverse symptomatic vasospasm. AVM: as above.

AVMs, arteriovenous malformations; CTA, computed tomography angiography; MRA, magnetic resonance angiography.

2. Obstruction of vertebrobasilar circulation—Occlusion of the **posterior cerebral artery** may lead to a thalamic syndrome in which contralateral hemisensory disturbance occurs, followed by the development of spontaneous pain and hyperesthesia. There is often a macular-sparing homonymous hemianopia and sometimes a mild, usually temporary, hemiparesis. Depending on the site of the lesion

and the collateral circulation, the severity of these deficits varies and other deficits may also occur, including involuntary movements and alexia. Occlusion of the main artery beyond the origin of its penetrating branches may lead solely to a macular-sparing hemianopia.

Vertebral artery occlusion below the origin of the anterior spinal and posterior inferior cerebellar arteries

may be clinically silent because the circulation is maintained by the other vertebral artery. If the remaining vertebral artery is congenitally small or severely atherosclerotic, however, a deficit similar to that of basilar artery occlusion is seen unless there is good collateral circulation from the anterior circulation through the circle of Willis. An obstruction of the **posterior inferior cerebellar artery** or an obstruction of the vertebral artery just before it branches to this vessel leads to the **lateral medullary syndrome**, characterized by vertigo and nystagmus (vestibular nucleus), ipsilateral spinothalamic sensory loss involving the face (trigeminal nucleus and tract), dysphagia (nucleus ambiguus), limb ataxia (inferior cerebellar peduncle), and Horner syndrome (descending sympathetic fibers), combined with contralateral spinothalamic sensory loss involving the limbs.

Occlusion of **both vertebral arteries** or the **basilar artery** leads to coma with pinpoint pupils, flaccid quadriplegia and sensory loss, and variable cranial nerve abnormalities. With partial basilar artery occlusion, there may be diplopia, visual loss, vertigo, dysarthria, ataxia, weakness or sensory disturbances in some or all of the limbs, and discrete cranial nerve palsies. In patients with hemiplegia of pontine origin, the eyes are often deviated to the paralyzed side, whereas in patients with a hemispheric lesion, the eyes commonly deviate from the hemiplegic side. When the small paramedian arteries arising from the basilar artery are occluded, contralateral hemiplegia and sensory deficit occur in association with an ipsilateral cranial nerve palsy at the level of the lesion.

Occlusion of any of the major **cerebellar arteries** produces vertigo, nausea, vomiting, nystagmus, and ipsilateral limb ataxia. Contralateral spinothalamic sensory loss in the limbs may also be present. Deafness due to cochlear infarction may follow occlusion of the anterior inferior cerebellar artery, which may also cause ipsilateral facial spinothalamic sensory loss and weakness. Massive cerebellar infarction may lead to obstructive hydrocephalus, coma, tonsillar herniation, and death.

B. Imaging

A CT scan of the head (without contrast) should be performed *immediately*, before the administration of aspirin or other antithrombotic agents, to exclude cerebral hemorrhage (Table 24–3). CT is relatively insensitive to acute ischemic stroke within the first 6–12 hours, and subsequent MRI with diffusion-weighted sequences helps define the distribution and extent of infarction as well as exclude tumor or other differential considerations. CT angiography of the head and neck should be performed to identify large vessel occlusions amenable to endovascular therapy in patients presenting within 6 hours of stroke onset and should be considered in those presenting between 6 and 24 hours, together with CT perfusion studies. Regardless of timing of presentation, imaging of the cervical vasculature is indicated as part of a search to identify the source of the stroke. In patients with a PFO and otherwise cryptogenic stroke, the intracranial vasculature must be imaged to rule out large vessel atherosclerosis before PFO closure can be considered.

C. Laboratory and Other Studies

Investigations should include a complete blood count, blood glucose determination, and fasting lipid panel. Serologic tests for syphilis and HIV infection may be included depending on the circumstances. Screening for antiphospholipid antibodies (lupus anticoagulants, anticardiolipin, and anti-beta2-glycoprotein antibodies); the factor V Leiden mutation; abnormalities of protein C, protein S, or antithrombin; or a prothrombin gene mutation is indicated only if a hypercoagulable disorder is suspected (eg, a young patient without apparent risk factors for stroke) or needs to be ruled out if PFO closure is under consideration. While elevated serum homocysteine is a risk factor for stroke, lowering homocysteine levels with vitamin supplementation has not been shown to decrease stroke risk, and therefore, routinely checking homocysteine is *not* recommended. Electrocardiography or continuous cardiac monitoring for at least 24 hours will help exclude a recent myocardial infarction or a cardiac arrhythmia that might be a source of embolization. While atrial fibrillation will be discovered in approximately 10% of patients with ischemic stroke during their hospitalization, it is estimated that an arrhythmia will be found in an additional 10% with prolonged ambulatory ECG monitoring after discharge; this testing is indicated in cases where atrial fibrillation is suspected (eg, nonlacunar stroke and left atrial enlargement on echocardiography or lack of intracranial or carotid atherosclerosis) but has not been demonstrated. Echocardiography (with agitated saline contrast) should be performed in cases of nonlacunar stroke to exclude valvular disease, right-to-left shunting, and cardiac thrombus. Blood cultures should be performed if endocarditis is suspected but are not required routinely. Examination of the cerebrospinal fluid is not always necessary but may be helpful if cerebral vasculitis or another inflammatory or infectious cause of stroke is suspected, but it should be delayed until after CT or MRI to exclude any risk for herniation due to mass effect.

Treatment

Management is divided into acute and chronic phases: the first is aimed at minimizing disability and the second at preventing recurrent stroke. A combination of thrombolysis and endovascular therapies is available to patients who present within 24 hours of stroke onset, determined by when the patient was last normal.

Intravenous thrombolytic therapy with recombinant tissue plasminogen activator (rtPA; 0.9 mg/kg to a maximum of 90 mg, with 10% given as a bolus over 1 minute and the remainder over 1 hour) improves the chance of recovery without significant disability at 90 days from 26% to 39% if given within 3 hours from stroke onset; it is still effective up to 4.5 hours from stroke onset. Treatment should be initiated as soon as possible; outcome is directly related to the time from stroke onset to treatment. Intravenous thrombolysis is approved in Europe for use up to 4.5 hours from stroke onset but only for up to 3 hours in the United States, although off-label use during the 3- to 4.5-hour window is standard. In patients with systolic pressure greater than 185 mm Hg or diastolic pressure greater than

110 mm Hg, the blood pressure should be lowered to less than 185/110 mm Hg with intravenous labetalol or nicardipine to enable rtPA administration. Due to the risk of hemorrhage, rtPA should not be used beyond 4.5 hours, or in other situations where it is medically contraindicated, although some evidence suggests patients with ischemic but not infarcted tissue identified by automated perfusion imaging or MRI may be treated up to 9 hours after onset or upon awakening with stroke symptoms.

Several randomized trials have demonstrated an increased likelihood of achieving functional independence after **endovascular mechanical embolectomy** by stent retrievers as an adjunct to intravenous rtPA. Patients with large vessel occlusion (about 20% of patients with acute ischemic stroke) in whom treatment can be initiated within 6 hours of stroke onset are eligible for embolectomy, as are patients who present between 6 hours and 24 hours and also have a large ischemic penumbra identified by perfusion CT, perfusion MRI, or diffusion-weighted MRI.

Early management of a completed stroke otherwise requires general supportive measures. Management in a **stroke care unit** has been shown to improve outcomes, likely due to early rehabilitation and prevention of medical complications. During the acute stage, there may be marked brain swelling and edema, with symptoms and signs of increasing intracranial pressure, an increasing neurologic deficit, or herniation syndrome. Elevated intracranial pressure is managed by head elevation and osmotic agents such as mannitol. Maintenance of an adequate cerebral perfusion pressure helps prevent further ischemia. Early decompressive hemicraniectomy (within 48 hours of stroke onset) for malignant middle cerebral artery infarctions reduces mortality and improves functional outcome. Attempts to lower the blood pressure of hypertensive patients during the acute phase (ie, within 72 hours) of a stroke should generally be *avoided* unless the purpose is to enable the safe administration of rtPA, as there is loss of cerebral autoregulation, and lowering the blood pressure may further compromise ischemic areas. However, if the systolic pressure exceeds 220 mm Hg, it can be lowered using intravenous labetalol or nicardipine with continuous monitoring to 170–200 mm Hg, and then after 72 hours, it can be reduced further to less than 140/90 mm Hg. Blood pressure augmentation is usually not necessary in patients with relative hypotension but maintenance of intravenous hydration is important.

Prophylactic and medical measures are discussed in the section on TIAs and should guide management. Once hemorrhage has been excluded by CT, **aspirin** (325 mg orally daily) is started immediately unless the patient received thrombolysis, in which case aspirin is initiated after a follow-up CT has ruled out thrombolytic-associated hemorrhage at 24 hours. **Dual antiplatelet therapy** should be used for 21 days in patients with minor stroke (National Institutes of Health Stroke Scale of 3 or less). **Anticoagulant** medications are started when indicated, as discussed in the section on TIAs. There is generally *no* advantage in delay, and the common fear of causing hemorrhage into a previously infarcted area is misplaced, since there is a far greater risk of further embolism to the cerebral circulation if treatment is withheld.

Physical therapy has an important role in the management of patients with impaired motor function. Passive movements at an early stage will help prevent contractures. As cooperation increases and some recovery begins, active movements will improve strength and coordination. In all cases, early mobilization and active rehabilitation are important. **Occupational therapy** may improve morale and motor skills, while **speech therapy** may help expressive aphasia or dysarthria. Because of the risk for dysphagia following stroke, access to food and drink is typically restricted until an appropriate swallowing evaluation; the head of the bed should be kept elevated to prevent aspiration. Urinary catheters should *not* be placed and, if placed, removed within 24–48 hours.

► Prognosis

The prognosis for survival after cerebral infarction is better than after cerebral or subarachnoid hemorrhage. Patients receiving treatment with rtPA are at least 30% more likely to have minimal or no disability at 3 months than those not treated by this means. Those treated with mechanical embolectomy are also at least 30% more likely to achieve functional independence. Loss of consciousness after a cerebral infarct implies a poorer prognosis than otherwise. The extent of the infarct governs the potential for rehabilitation. Patients who have had a cerebral infarct are at risk for additional strokes and for myocardial infarcts. The prophylactic measures discussed earlier reduce this risk. Antiplatelet therapy reduces the recurrence rate by 30% among patients without a cardiac cause for the stroke who are not candidates for carotid endarterectomy. Nevertheless, the cumulative risk of recurrence of noncardioembolic stroke is still 3–7% annually. Management is focused on palliative care when meaningful recovery from massive strokes is unlikely (see Chapter 5).

► When to Refer

All patients should be referred.

► When to Admit

All patients should be hospitalized, preferably in a stroke care unit.

Albers GW et al; DEFUSE 3 Investigators. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med*. 2018;378:708. [PMID: 29364767]

Nogueira RG et al; DAWN Trial Investigators. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med*. 2018;378:11. [PMID: 29129157]

Powers WJ et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2019;50:e344. [PMID: 31662037]

3. Intracerebral Hemorrhage

Spontaneous, nontraumatic intracerebral hemorrhage in patients with no angiographic evidence of an associated vascular anomaly (eg, aneurysm or angioma) is usually due

to hypertension. The pathologic basis for hemorrhage is probably the presence of microaneurysms that develop on perforating vessels in hypertensive patients. Hypertensive intracerebral hemorrhage occurs most frequently in the basal ganglia, pons, thalamus, and cerebellum, and less commonly in the cerebral white matter. Hemorrhage may extend into the ventricular system or subarachnoid space, and signs of meningeal irritation are then found. In older adults, cerebral amyloid angiopathy is another important and frequent cause of hemorrhage, which is usually lobar in distribution, sometimes recurrent, and associated with a better immediate prognosis than hypertensive hemorrhage. Arteriovenous malformations are an important cause of intracerebral hemorrhage in younger patients.

Other causes of nontraumatic intracerebral hemorrhage include hematologic and bleeding disorders (eg, leukemia, thrombocytopenia, hemophilia, or disseminated intravascular coagulation), anticoagulant therapy, liver disease, high alcohol intake, cocaine and methamphetamine abuse, herpes simplex encephalitis, vasculitis, moyamoya disease, reversible cerebral vasoconstriction syndrome, and primary or secondary brain tumors. There is also an association with advancing age and male sex. Bleeding is primarily into the subarachnoid space when it occurs from an intracranial aneurysm, but it may be partly intraparenchymal as well. Hemorrhage can also occur into arterial and venous cerebral infarcts.

► Clinical Findings

A. Symptoms and Signs

With hemorrhage into the cerebral hemisphere, consciousness is initially lost or impaired in about one-half of patients. Vomiting occurs very frequently at the onset of bleeding, and headache is sometimes present. Focal symptoms and signs then develop, depending on the site of the hemorrhage. With hypertensive hemorrhage, there is generally a rapidly evolving neurologic deficit with hemiplegia or hemiparesis. A hemisensory disturbance is also present with more deeply placed lesions. With lesions of the putamen, loss of conjugate lateral gaze may be conspicuous. With thalamic hemorrhage, there may be a loss of upward gaze, downward or skew deviation of the eyes, lateral gaze palsies, and pupillary inequalities.

Cerebellar hemorrhage may present with sudden onset of nausea and vomiting, dysequilibrium, ataxia of gait, limbs, or trunk; headache; and loss of consciousness that may terminate fatally within 48 hours. Pontine hemorrhage causes some combination of lateral conjugate gaze palsies to the side of the lesion; small reactive pupils; contralateral hemiplegia; peripheral facial weakness; and periodic respiration. These signs may be bilateral with larger pontine hemorrhage, and the patient may become locked in, with quadriplegia and preserved consciousness.

B. Imaging

CT scanning (without contrast) is important not only in confirming that hemorrhage has occurred but also in determining the size and site of the hematoma. MRI is

equally sensitive when magnetic susceptibility weighted sequences (eg, gradient echo) are used. If the patient's condition permits further intervention, CT angiography, MR angiography, or cerebral angiography may be undertaken to determine whether an aneurysm or arteriovenous malformation is present. In patients under age 55 with lobar hemorrhage and no history of hypertension, a contrast-enhanced MRI may indicate a nonhypertensive cause, such as an underlying neoplasm.

C. Laboratory and Other Studies

A complete blood count, platelet count, prothrombin and partial thromboplastin times, liver biochemical tests, and kidney function tests may reveal a predisposing cause for the hemorrhage. *Lumbar puncture is contraindicated* because it may precipitate a herniation syndrome in patients with a large hematoma, and CT scanning is superior in detecting intracerebral hemorrhage.

► Treatment

Patients should be admitted to an intensive care unit for observation and supportive care. The systolic blood pressure should be lowered to 140 mm Hg with intravenous labetalol or nicardipine, although randomized trials targeting systolic blood pressures of less than 140 mm Hg and less than 180 mm Hg have not shown a difference in outcomes. Thrombocytopenia should be treated with platelet transfusion; the specific threshold for treatment and the goal platelet count after transfusion vary with patient characteristics and provider experience. Coagulopathies should be reversed using fresh frozen plasma, prothrombin complex concentrates, vitamin K, or specific reversal agents (eg, protamine for heparin; idarucizumab for dabigatran; andandexanet alfa for apixaban, betrixaban, edoxaban, and rivaroxaban). Hemostatic therapy with recombinant activated factor VII in patients without underlying coagulopathy has not improved survival or functional outcome. Intracranial pressure may require monitoring and osmotic therapy. Ventricular drainage may be required in patients with intraventricular hemorrhage and acute hydrocephalus. Decompression may be helpful when a superficial hematoma in cerebral white matter is exerting a mass effect and causing incipient herniation. In patients with cerebellar hemorrhage who are deteriorating neurologically or who have brainstem compression or hydrocephalus, prompt surgical evacuation of the hematoma is appropriate because spontaneous unpredictable deterioration may otherwise lead to a fatal outcome and because operative treatment may lead to complete resolution of the clinical deficit. The treatment of underlying structural lesions or bleeding disorders depends on their nature. There is no specific treatment for cerebral amyloid angiopathy.

► When to Refer

All patients should be referred.

► When to Admit

All patients should be hospitalized.

Hostettler IC et al. Intracerebral hemorrhage: an update on diagnosis and treatment. Expert Rev Neurother. 2019;19:679. [PMID: 31188036]

4. Spontaneous Subarachnoid Hemorrhage



ESSENTIALS OF DIAGNOSIS

- ▶ Sudden (“thunderclap”) severe headache.
- ▶ Signs of meningeal irritation usually present.
- ▶ Obtundation is common.
- ▶ Focal deficits frequently absent.

► General Considerations

Between 5% and 10% of strokes are due to subarachnoid hemorrhage. **Trauma** is the most common cause of subarachnoid hemorrhage, the prognosis of which depends on the severity of the head injury. Spontaneous (nontraumatic) subarachnoid hemorrhage frequently results from the rupture of an **arterial saccular (“berry” aneurysm** or from an **arteriovenous malformation**.

► Clinical Findings

A. Symptoms and Signs

Subarachnoid hemorrhage has a characteristic clinical picture. Its onset is with sudden (“**thunderclap**”) headache of a severity never experienced previously by the patient. This may be followed by nausea and vomiting and by a loss or impairment of consciousness that can either be transient or progress inexorably to deepening coma and death. If consciousness is regained, the patient is often confused and irritable and may show other symptoms of an altered mental status. Neurologic examination generally reveals nuchal rigidity and other signs of meningeal irritation, except in deeply comatose patients.

Most aneurysms are asymptomatic until they rupture, but they may cause a focal neurologic deficit by compressing adjacent structures. Occasional patients with aneurysms have headaches, sometimes accompanied by nausea and neck stiffness, a few hours or days before massive subarachnoid hemorrhage occurs. This has been attributed to “warning leaks” of a small amount of blood from the aneurysm.

A higher risk of subarachnoid hemorrhage is associated with older age, female sex, non-White ethnicity, hypertension, tobacco smoking, high alcohol consumption (exceeding 150 g per week), previous symptoms, posterior circulation aneurysms, and larger aneurysms. Focal neurologic signs are usually absent but, when present, may relate either to a focal intracerebral hematoma (from arteriovenous malformations) or to ischemia in the territory of the vessel with a ruptured aneurysm.

B. Imaging

A CT scan (preferably with CT angiography) should be performed immediately to confirm that hemorrhage has

occurred and to search for clues regarding its source. It is preferable to MRI because it is faster and more sensitive in detecting hemorrhage in the first 24 hours. CT findings sometimes are normal in patients with suspected hemorrhage, and the cerebrospinal fluid must then be examined for the presence of blood or xanthochromia before the possibility of subarachnoid hemorrhage is discounted.

Cerebral arteriography is undertaken to determine the source of bleeding. In general, bilateral carotid and vertebral arteriography are necessary because aneurysms are often multiple, while arteriovenous malformations may be supplied from several sources. The procedure allows an interventional radiologist to treat an underlying aneurysm or arteriovenous malformation by various techniques. If arteriograms show no abnormality, the examination should be repeated after 2 weeks because vasospasm or thrombus may have prevented detection of an aneurysm or other vascular anomaly during the initial study. CT or MR angiography may also be revealing but is less sensitive than conventional arteriography.

C. Laboratory and Other Studies

The cerebrospinal fluid demonstrates an elevated red blood cell count. Subarachnoid hemorrhage can be differentiated from a traumatic lumbar puncture by the lack of clearing of red blood cells from the first and fourth tube of cerebrospinal fluid or by the presence of xanthochromia, which occurs due to lysis of red blood cells and takes at least 2 hours to develop. The absolute red blood cell count is also helpful: in the absence of xanthochromia, a red blood cell count of less than $2000 \times 10^6/\text{L}$ is very unlikely to be due to subarachnoid hemorrhage. Electrocardiographic evidence of arrhythmias or myocardial ischemia has been well described and probably relates to excessive sympathetic activity. Peripheral leukocytosis and transient glycosuria are also common findings.

► Treatment

All patients should be hospitalized and seen by a neurologist. The measures outlined below in the section on stupor and coma are applied to comatose patients. Conscious patients are confined to bed, advised against any exertion or straining, treated symptomatically for headache and anxiety, and given laxatives or stool softeners. The systolic blood pressure should be lowered to 140 mm Hg until the aneurysm is treated definitively. Seizure prophylaxis is not necessary unless a convulsion has occurred (see Table 24–2). Patients are generally hospitalized for at least 14 days to monitor, prevent, and treat vasospasm.

The major aim of treatment is to prevent further hemorrhage. The risk of further hemorrhage from a ruptured aneurysm is greatest within a few days of the first hemorrhage; approximately 20% of patients will have further bleeding within 2 weeks and 40% within 6 months. Definitive treatment, ideally within 2 days of the hemorrhage, requires surgical clipping of the aneurysm or endovascular treatment by coil embolization; the latter is sometimes feasible even for inoperable aneurysms and has a lower morbidity than surgery.

► Complications

Spontaneous subarachnoid hemorrhage may result in severe complications, so monitoring is necessary, usually in an intensive care unit. Hemiplegia or other focal deficit sometimes may follow aneurysmal bleeding after a delay of 2–14 days due to focal arterial spasm. The etiology of **vasospasm** is uncertain and likely multifactorial, and it sometimes leads to significant cerebral ischemia or infarction and may further aggravate any existing increase in intracranial pressure. Transcranial Doppler ultrasound may be used to screen noninvasively for vasospasm, but conventional arteriography is required to document and treat vasospasm when the clinical suspicion is high. Nimodipine has been shown to reduce the incidence of ischemic deficits from arterial spasm; a dose of 60 mg every 4 hours orally for 21 days is given prophylactically to all patients. After surgical obliteration of all aneurysms, symptomatic vasospasm may also be treated by intravascular volume expansion and induced hypertension; transluminal balloon angioplasty of involved intracranial vessels is also helpful.

Acute hydrocephalus, which sometimes occurs due to cerebrospinal fluid outflow disruption by the subarachnoid blood, should be suspected if the patient deteriorates clinically; a repeat CT scan should be obtained. Acute hydrocephalus frequently causes intracranial hypertension severe enough to require temporary, and less commonly prolonged or permanent, intraventricular cerebrospinal fluid shunting. **Cerebral salt-wasting** is another complication of subarachnoid hemorrhage that may develop abruptly during the first several days of hospitalization. The resulting hyponatremia and cerebral edema may exacerbate intracranial hypertension and may require carefully titrated treatment with oral sodium chloride or intravenous hyperosmotic sodium solution. Daily measurement of the serum sodium level allows for the early detection of this complication. **Hypopituitarism** may occur as a late complication of subarachnoid hemorrhage.

Etminan N et al. Neurovascular disease, diagnosis, and therapy: subarachnoid hemorrhage and cerebral vasospasm. *Handb Clin Neurol.* 2021;176:135. [PMID: 33272393]

Lindgren A et al. Endovascular coiling versus neurosurgical clipping for people with aneurysmal subarachnoid hemorrhage. *Cochrane Database Syst Rev.* 2018;8:CD003085. [PMID: 30110521]

5. Intracranial Aneurysm



ESSENTIALS OF DIAGNOSIS

- Subarachnoid hemorrhage or focal deficit.
- Abnormal imaging studies.

► General Considerations

Saccular aneurysms (“berry” aneurysms) tend to occur at arterial bifurcations, are frequently multiple (20% of cases), and are usually asymptomatic. They are associated with

polycystic kidney disease, moyamoya disease, familial aldosteronism type 1, and coarctation of the aorta. Risk factors for aneurysm formation include cigarette smoking, hypertension, and female sex. Most aneurysms are located on the anterior part of the circle of Willis—particularly on the anterior or posterior communicating arteries, at the bifurcation of the middle cerebral artery, and at the bifurcation of the internal carotid artery. Mycotic aneurysms resulting from septic embolism occur in more distal vessels and often at the cortical surface. The most significant complication of intracranial aneurysms is a subarachnoid hemorrhage, which is discussed in the preceding section.

► Clinical Findings

A. Symptoms and Signs

Aneurysms may cause a focal neurologic deficit by compressing adjacent structures. However, most are asymptomatic or produce only nonspecific symptoms until they rupture, at which time subarachnoid hemorrhage results. Its manifestations, complications, and management were outlined in the preceding section.

B. Imaging

Definitive evaluation is by digital subtraction angiography (bilateral carotid and vertebral studies), which generally indicates the size and site of the lesion, sometimes reveals multiple aneurysms, and may show arterial spasm if rupture has occurred. Visualization by CT or MR angiography is not usually adequate if operative treatment is under consideration because lesions may be multiple and small lesions are sometimes missed, but these modalities can be used to screen patients who have two or more first-degree relatives with intracranial aneurysms.

► Treatment

The major aim of treatment is to *prevent hemorrhage*. Management of ruptured aneurysms was described in the section on subarachnoid hemorrhage. Symptomatic but unruptured aneurysms merit prompt treatment, either surgically or by endovascular techniques. The decision to treat or monitor asymptomatic aneurysms discovered incidentally is complicated and depends on aneurysm size, location, risk factors for rupture, and treatment-related morbidity; risk scores to guide decision-making are available.

► When to Refer

All patients should be referred.

► When to Admit

- All patients with a subarachnoid hemorrhage.
- All patients for detailed imaging.
- All patients undergoing surgical or endovascular treatment.

Hackenberg KAM et al. Neurovascular disease, diagnosis, and therapy: brain aneurysms. *Handb Clin Neurol.* 2021;176:121. [PMID: 33272392]

6. Arteriovenous Malformations



ESSENTIALS OF DIAGNOSIS

- ▶ Sudden onset of subarachnoid and intracerebral hemorrhage.
- ▶ Distinctive neurologic signs reflect the region of the brain involved.
- ▶ Signs of meningeal irritation in patients presenting with subarachnoid hemorrhage.
- ▶ Seizures or focal deficits may occur.

► General Considerations

Arteriovenous malformations are congenital vascular malformations that result from a localized maldevelopment of part of the primitive vascular plexus and consist of abnormal arteriovenous communications without intervening capillaries. They vary in size, ranging from massive lesions that are fed by multiple vessels and involve a large part of the brain to lesions so small that they are hard to identify at arteriography, surgery, or autopsy. In approximately 10% of cases, there is an associated arterial aneurysm, while 1–2% of patients presenting with aneurysms have associated arteriovenous malformations. Clinical presentation may relate to hemorrhage from the malformation or an associated aneurysm or may relate to cerebral ischemia due to diversion of blood by the anomalous arteriovenous shunt or due to venous stagnation. Regional maldevelopment of the brain, compression or distortion of adjacent cerebral tissue by enlarged anomalous vessels, and progressive gliosis due to mechanical and ischemic factors may also be contributory.

► Clinical Findings

Most cerebral arteriovenous malformations are supratentorial, usually lying in the territory of the middle cerebral artery. Up to 70% bleed at some point in their natural history, most commonly before the patient reaches the age of 40 years. Arteriovenous malformations that have bled once are more likely to bleed again, at an approximate rate of 4.5% annually. A higher risk of bleeding is also observed if there is an associated aneurysm, deep venous drainage, or deep brain location; size of the malformation and sex are not associated with risk of hemorrhage.

A. Symptoms and Signs

Initial symptoms consist of hemorrhage in 30–60% of cases, recurrent seizures in 20–40%, headache in 5–25%, and miscellaneous complaints (including focal deficits) in 10–15%. Hemorrhage is commonly intracerebral as well as into the subarachnoid space and is fatal in about 10% of cases. Seizures are more likely with frontal or parietal arteriovenous malformations. Headaches are especially likely when the external carotid arteries are involved in the malformation. These sometimes simulate migraine, but more

commonly are nonspecific in character, with nothing about them to suggest an underlying structural lesion. Brainstem and cerebellar arteriovenous malformations may cause obstructive hydrocephalus.

In patients presenting with subarachnoid hemorrhage, examination may reveal an abnormal mental status and signs of meningeal irritation. Additional findings may help localize the lesion and sometimes indicate that intracranial pressure is increased. A cranial bruit always suggests the possibility of a cerebral arteriovenous malformation, but bruits may also be found with aneurysms, meningiomas, acquired arteriovenous fistulas, and arteriovenous malformations involving the scalp, calvarium, or orbit. Bruits are best heard over the ipsilateral eye or mastoid region and are of some help in lateralization but of no help in localization. Absence of a bruit *does not exclude* the possibility of arteriovenous malformation.

B. Imaging

In patients with suspected hemorrhage, CT scanning indicates whether subarachnoid or intracerebral bleeding has recently occurred, helps localize its source, and may reveal the arteriovenous malformation. When intracranial hemorrhage is confirmed but the source of hemorrhage is not evident on the CT scan, arteriography is necessary to exclude aneurysm or arteriovenous malformation. MR and CT angiography are not sensitive enough for this purpose. Even if the findings on CT scan suggest arteriovenous malformation, arteriography is required to establish the nature of the lesion with certainty and to determine its anatomic features so that treatment can be planned. The examination must generally include bilateral opacification of the internal and external carotid arteries and the vertebral arteries.

In patients presenting without hemorrhage, CT scan or MRI usually reveals the underlying abnormality, and MRI frequently also shows evidence of old or recent hemorrhage that may have been asymptomatic. The nature and detailed anatomy of any focal lesion identified by these means are delineated by angiography, especially if operative treatment is under consideration.

► Treatment

Surgical treatment to prevent further hemorrhage is justified in patients with arteriovenous malformations that have bled, provided that the lesion is accessible and the patient has a reasonable life expectancy. Surgical treatment is also appropriate if intracranial pressure is increased and to prevent further progression of a focal neurologic deficit. In patients presenting solely with seizures, anticonvulsant treatment is usually sufficient (Table 24–2), and operative treatment is unnecessary unless seizures cannot be controlled medically.

Definitive operative treatment consists of excision of the arteriovenous malformation if it is surgically accessible. Stereotactic radiosurgery is used to treat inoperable cerebral arteriovenous malformations. Arteriovenous malformations that are inoperable because of their location are sometimes treated solely by embolization; although the risk of hemorrhage is not reduced, neurologic deficits may

be stabilized or even reversed by this procedure. Embolization is more commonly performed as an adjunct to surgery or radiosurgery; it is also used to treat aneurysms associated with the arteriovenous malformations.

► When to Refer

All patients should be referred.

► When to Admit

- All patients with a subarachnoid or cerebral hemorrhage.
- All patients for detailed imaging.
- All patients undergoing surgical or endovascular treatment.

Rutledge C et al. Brain arteriovenous malformations. *Handb Clin Neurol*. 2021;176:171. [PMID: 33272394]

7. Intracranial Venous Thrombosis

Intracranial venous thrombosis may occur in association with intracranial or maxillofacial infections, hypercoagulable states, polycythemia, sickle cell disease, cyanotic congenital heart disease, and in pregnancy or during the puerperium. Genetic factors are also important. The disorder is characterized by headache, focal or generalized convulsions, drowsiness, confusion, increased intracranial pressure, and focal neurologic deficits—and sometimes by evidence of meningeal irritation. The diagnosis is confirmed by CT or MR venography or angiography.

Treatment includes anticonvulsants if seizures have occurred (Table 24–2) and—if necessary—measures to reduce intracranial pressure. Anticoagulation with dose-adjusted intravenous heparin or weight-adjusted subcutaneous low-molecular-weight heparin, followed by oral warfarin anticoagulation for 6 months reduces morbidity and mortality of venous sinus thrombosis. Dabigatran showed similar efficacy to warfarin in one randomized trial and may be an acceptable alternative. Concomitant intracranial hemorrhage related to the venous thrombosis does not contraindicate heparin therapy. In cases refractory to heparin, endovascular techniques including catheter-directed thrombolytic therapy (urokinase) and thrombectomy are sometimes helpful but may increase the risk for major hemorrhage.

► When to Refer

All patients should be referred.

► When to Admit

All patients should be hospitalized.

Ferro JM et al; RE-SPECT CVT Study Group. Safety and efficacy of dabigatran etexilate vs dose-adjusted warfarin in patients with cerebral venous thrombosis: a randomized clinical trial. *JAMA Neurol*. 2019;76:1457. [PMID: 31479105]

8. Spinal Cord Vascular Diseases



ESSENTIALS OF DIAGNOSIS

- ▶ Sudden onset of back or limb pain and neurologic deficit in limbs.
- ▶ Motor, sensory, or reflex changes in limbs depending on level of lesion.
- ▶ Imaging studies distinguish between infarct and hematoma.

► Infarction of the Spinal Cord

Infarction of the spinal cord is rare. It typically occurs in the territory of the *anterior spinal artery* because this vessel, which supplies the anterior two-thirds of the cord, is itself supplied by only a limited number of feeders. Infarction usually results from interrupted flow in one or more of these feeders, eg, with aortic dissection, aortic aneurysm, aortography, polyarteritis, severe hypotension, or after surgical repair of the thoracic or abdominal aorta. The paired posterior spinal arteries, by contrast, are supplied by numerous arteries at different levels of the cord. Spinal cord hypoperfusion may lead to a central cord syndrome with distal weakness of lower motor neuron type and loss of pain and temperature appreciation, with preserved posterior column function.

Since the anterior spinal artery receives numerous feeders in the cervical region, infarcts almost always occur caudally. Clinical presentation is characterized by acute onset of flaccid, areflexive paraparesis that evolves after a few days or weeks into a spastic paraparesis with extensor plantar responses. There is an accompanying dissociated sensory loss, with impairment of appreciation of pain and temperature but preservation of sensations of vibration and joint position.

The risk of spinal cord infarction in the setting of abdominal aortic surgery and thoracic endovascular repair may be reduced by intraoperative cerebrospinal fluid drainage through a catheter placed in the lumbar subarachnoid space to reduce intraspinal pressure. If signs of infarction are noted after surgery, blood pressure augmentation for 24–48 hours in addition to lumbar drainage has been noted anecdotally to improve outcomes. Treatment is otherwise symptomatic.

► Epidural or Subdural Hemorrhage

Epidural or subdural hemorrhage may lead to sudden severe back pain followed by an acute compressive myopathy necessitating urgent spinal MRI or myelography and surgical evacuation. It may occur in patients with bleeding disorders or those who are taking anticoagulants, sometimes following trauma or lumbar puncture. Epidural hemorrhage may also be related to a vascular malformation or tumor deposit.

► Spinal Dural Arteriovenous Fistulae

Spinal dural arteriovenous fistulae are congenital lesions that present with spinal subarachnoid hemorrhage or

myeloradiculopathy. Since most of these malformations are located in the thoracolumbar region, they lead to motor and sensory disturbances in the legs and to sphincter disorders. Pain in the legs or back is often severe. Examination reveals an upper, lower, or mixed motor deficit in the legs; sensory deficits are also present and are usually extensive, although occasionally they are confined to a radicular distribution. Cervical spinal dural arteriovenous fistulae lead also to symptoms and signs in the arms. Spinal MRI may not detect the spinal dural arteriovenous fistula, although most cases show either T2 hyperintensity in the cord or perimedullary flow voids. Myelography (performed with the patient prone and supine) may detect serpiginous filling defects due to enlarged vessels. Selective spinal arteriography is required to confirm the diagnosis and plan treatment. Most lesions are extramedullary, are posterior to the cord (lying either intradurally or extradurally), and can easily be treated by ligation of feeding vessels and excision of the fistulous anomaly or by embolization procedures. Delay in treatment may lead to increased and irreversible disability or to death from recurrent subarachnoid hemorrhage.

► When to Refer

All patients should be referred.

► When to Admit

All patients should be hospitalized.

Goyal A et al. Outcomes following surgical versus endovascular treatment of spinal dural arteriovenous fistula: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry*. 2019;90:1139. [PMID: 31142659]

INTRACRANIAL & SPINAL MASS LESIONS

1. Primary Intracranial Tumors



ESSENTIALS OF DIAGNOSIS

- ▶ Generalized or focal disturbance of cerebral function, or both.
- ▶ Increased intracranial pressure in some patients.
- ▶ Neuroradiologic evidence of space-occupying lesion.

► General Considerations

Roughly one-third of all primary intracranial neoplasms (Table 24–4) are meningiomas, one-quarter are gliomas, and the remainder are pituitary adenomas (see Chapter 26), neurofibromas, and other tumors. Certain tumors, especially neurofibromas, hemangioblastomas, and retinoblastomas, may have a familial basis, and congenital factors bear on the development of craniopharyngiomas. Tumors may occur at any age, but certain gliomas show particular age predilections.

► Clinical Findings

A. Symptoms and Signs

Intracranial tumors typically present with headache, seizures, or focal neurologic deficits. New headaches or symptoms of elevated intracranial pressure, such as headaches awaking a patient from sleep or worsening with Valsalva maneuver, cough, or recumbency, are suggestive of brain tumor. Intracranial tumors may also lead to a generalized disturbance of cerebral function with personality changes, intellectual decline, emotional lability, nausea, and malaise.

1. Frontal lobe lesions—Tumors of the frontal lobe often lead to progressive intellectual decline, slowing of mental activity, personality changes, and contralateral grasp reflexes. They may lead to expressive aphasia if the posterior part of the left inferior frontal gyrus is involved. Anosmia may also occur as a consequence of pressure on the olfactory nerve. Precentral lesions may cause focal motor seizures or contralateral pyramidal deficits.

2. Temporal lobe lesions—Tumors of the uncinate region may be manifested by seizures with olfactory or gustatory hallucinations, motor phenomena such as licking or smacking of the lips, and some impairment of external awareness without actual loss of consciousness. Temporal lobe lesions also lead to depersonalization, emotional changes, behavioral disturbances, sensations of *déjà vu* or *jamais vu*, micropsia or macropsia (objects appear smaller or larger than they are), visual field defects (crossed upper quadrantanopia), and auditory illusions or hallucinations. Left-sided lesions may lead to dysnomia and receptive aphasia, while right-sided involvement sometimes disturbs the perception of musical notes and melodies.

3. Parietal lobe lesions—Tumors in this location characteristically cause contralateral disturbances of sensation and may cause sensory seizures, sensory loss or inattention, or some combination of these symptoms. The sensory loss is cortical in type and involves postural sensibility and tactile discrimination, so that the appreciation of shape, size, weight, and texture is impaired. Objects placed in the hand may not be recognized (*astereognosis*). Extensive parietal lobe lesions may produce contralateral hyperesthesia and spontaneous pain (*thalamic syndrome*). Involvement of the optic radiation leads to a contralateral homonymous field defect that sometimes consists solely of lower quadrantanopia. Lesions of the left angular gyrus cause **Gerstmann syndrome** (a combination of alexia, agraphia, acalculia, right-left confusion, and finger agnosia), whereas involvement of the left submarginal gyrus causes ideational apraxia. Anosognosia (the denial, neglect, or rejection of a paralyzed limb) is seen in patients with lesions of the nondominant (right) hemisphere. Constructional apraxia and dressing apraxia may also occur with right-sided lesions.

4. Occipital lobe lesions—Tumors of the occipital lobe characteristically produce contralateral homonymous hemianopia or a partial field defect. With left-sided or bilateral lesions, there may be visual agnosia both for objects and for colors, while irritative lesions on either side

Table 24–4. Primary intracranial tumors (listed by major histology grouping and by incidence within each group).

Tumor	Clinical Features	Treatment and Prognosis
Tumors of Meninges		
Meningioma	Originates from the dura mater or arachnoid; compresses rather than invades adjacent neural structures. Increasingly common with advancing age. Tumor size varies greatly. Symptoms vary with tumor site—eg, unilateral proptosis (sphenoidal ridge); anosmia and optic nerve compression (olfactory groove). Tumor is usually benign and readily detected by CT scanning; may lead to calcification and bone erosion visible on plain radiographs of skull.	Treatment is surgical. Tumor may recur if removal is incomplete.
Tumors of Neuroepithelial Origin		
Glioblastoma multiforme	Presents commonly with nonspecific complaints and increased intracranial pressure. As it grows, focal deficits develop. O ⁶ -methylguanine-DNA methyltransferase promoter methylation positivity (seen in 40% of cases) and isocitrate dehydrogenase 1/2 mutations (seen in 10% of cases) carry better prognosis.	Course is rapidly progressive, with poor prognosis (< 20% survival at 2 years). Total surgical removal is usually not possible. Radiation therapy and temozolamide may prolong survival. Tumor treatment fields added to temozolamide after completion of radiation therapy prolong survival.
Astrocytoma	Presentation similar to glioblastoma multiforme but course more protracted, often over several years. Cerebellar astrocytoma may have a more benign course. Isocitrate dehydrogenase 1/2 mutations (seen in a majority of cases) carry better prognosis in grade II and III tumors.	Prognosis is variable. By the time of diagnosis, total excision is usually impossible; tumor may be radiosensitive and temozolamide is also helpful in grade II and III tumors. In cerebellar astrocytoma, total surgical removal is often possible.
Ependymoma	Glioma arising from the ependyma of a ventricle, especially the fourth ventricle; leads to early signs of increased intracranial pressure. Arises also from central canal of cord.	Tumor is best treated surgically if possible. Radiation therapy may be used for residual tumor.
Oligodendrogioma	Slow-growing. Usually arises in cerebral hemisphere in adults. Calcification may be visible on skull radiograph. Co-deletion of 1p/19q and isocitrate dehydrogenase 1/2 mutation required for diagnosis.	Treatment is surgical and usually successful. Radiation and chemotherapy (temozolamide or procarbazine, lomustine, and vincristine) are used in grade II and III tumors.
Brainstem glioma	Presents during childhood with cranial nerve palsies and then with long tract signs in the limbs. Signs of increased intracranial pressure occur late.	Tumor is inoperable; treatment is by irradiation and shunt for increased intracranial pressure.
Neuronal and mixed neuronal-glia tumors	Slow-growing; usually arise in cerebral hemispheres; often associated with seizures. Some are benign (eg, dysembryoplastic neuroepithelial tumors) and some have malignant potential (eg, ganglioglioma).	Resection is not always necessary for benign tumors unless seizures are medically refractory, but is indicated for those with malignant potential.
Medulloblastoma	Seen most frequently in children. Generally arises from roof of fourth ventricle and leads to increased intracranial pressure accompanied by brainstem and cerebellar signs. May seed subarachnoid space. Wingless activated tumors carry best prognosis (> 90% 5-year survival).	Treatment consists of surgery combined with radiation therapy and chemotherapy; 5-year survival exceeds 70%. Wingless activated tumors may require less aggressive treatment.
Pineal tumor	Presents with increased intracranial pressure, sometimes associated with impaired upward gaze (Parinaud syndrome) and other deficits indicative of midbrain lesion.	Ventricular decompression by shunting is followed by surgical approach to tumor; irradiation is indicated if tumor is malignant. Prognosis depends on histopathologic findings and extent of tumor.
Tumors of the Sellar Region		
Pituitary adenoma	Functioning adenomas present with symptoms of hormone secretion; nonfunctioning adenomas present with symptoms of local mass effect (eg, bitemporal hemianopsia, hypopituitarism) or are found incidentally.	Prolactin-secreting adenomas are treated with bromocriptine or cabergoline. Others are surgically resected. Pituitary hormone replacement may be required.
Cranipharyngioma	Originates from remnants of Rathke pouch above the sella, depressing the optic chiasm. May present at any age but usually in childhood, with endocrine dysfunction and bitemporal visual field defects.	Treatment is surgical, but total removal may not be possible. Radiation may be used for residual tumor.

(continued)

Table 24–4. Primary intracranial tumors (listed by major histology grouping and by incidence within each group). (continued)

Tumor	Clinical Features	Treatment and Prognosis
Germ cell tumors (germinomas and nongerminomatous germ cell tumors)	Two most common locations are pineal and suprasellar regions. The pineal region presentation is as described in pineal tumors, above. Suprasellar tumors present with hypothalamic and pituitary dysfunction such as diabetes insipidus, delayed or precocious puberty, or growth hormone deficiency.	Germinomas are treated with radiation; prognosis is good for localized tumors. Chemotherapy is added for nongerminomatous germ cell tumors.
Tumors of Cranial and Spinal Nerves		
Acoustic neurinoma (also referred to as acoustic neuroma)	Ipsilateral hearing loss is most common initial symptom. Subsequent symptoms may include tinnitus, headache, vertigo, facial weakness or numbness, and long tract signs. (May be familial and bilateral when related to neurofibromatosis.) Most sensitive screening tests are MRI and brainstem auditory evoked potential.	Treatment is excision by translabyrinthine surgery, craniectomy, or a combined approach. Outcome is usually good.
Lymphomas		
Primary cerebral lymphoma	Associated with AIDS and other immunodeficient states. Presentation may be with focal deficits or with disturbances of cognition and consciousness. May be indistinguishable from cerebral toxoplasmosis.	Treatment is high-dose methotrexate and corticosteroids followed by radiation therapy. Prognosis depends on CD4 count at diagnosis.
Unclassified		
Cerebellar hemangioblastoma	Presents with dysequilibrium, ataxia of trunk or limbs, and signs of increased intracranial pressure. Sometimes familial. May be associated with retinal and spinal vascular lesions, polycythemia, and renal cell carcinoma.	Treatment is surgical. Radiation is used for residual tumor.

can cause unformed visual hallucinations. Bilateral occipital lobe involvement causes cortical blindness in which there is preservation of pupillary responses to light and lack of awareness of the defect by the patient. There may also be loss of color perception, prosopagnosia (inability to identify a familiar face), simultagnosia (inability to integrate and interpret a composite scene as opposed to its individual elements), and Balint syndrome (failure to turn the eyes to a particular point in space, despite preservation of spontaneous and reflex eye movements). The denial of blindness or a field defect constitutes Anton syndrome.

5. Brainstem and cerebellar lesions—Brainstem lesions lead to cranial nerve palsies, ataxia, incoordination, nystagmus, and pyramidal and sensory deficits in the limbs on one or both sides. Intrinsic brainstem tumors, such as gliomas, tend to produce an increase in intracranial pressure only late in their course. Cerebellar tumors produce marked ataxia of the trunk if the vermis cerebelli is involved and ipsilateral appendicular deficits (ataxia, incoordination, and hypotonia of the limbs) if the cerebellar hemispheres are affected.

6. Herniation syndromes—If the pressure is increased in a particular cranial compartment, brain tissue may herniate into a compartment with lower pressure. The most familiar syndrome is herniation of the temporal lobe uncus through the tentorial hiatus, which causes compression of the third cranial nerve, midbrain, and posterior cerebral artery. The earliest sign of this is ipsilateral pupillary dilation, followed by stupor, coma, decerebrate posturing, and respiratory arrest. Another important herniation syndrome consists of

displacement of the cerebellar tonsils through the foramen magnum, which causes medullary compression leading to apnea, circulatory collapse, and death.

7. False localizing signs—Tumors may lead to neurologic signs other than by direct compression or infiltration, thereby leading to errors of clinical localization. These false localizing signs include third or sixth nerve palsy and bilateral extensor plantar responses produced by herniation syndromes, and an extensor plantar response occurring ipsilateral to a hemispheric tumor as a result of compression of the opposite cerebral peduncle against the tentorium.

B. Imaging

MRI with gadolinium enhancement is the preferred method to detect the lesion and to define its location, shape, and size; the extent to which normal anatomy is distorted; and the degree of any associated cerebral edema or mass effect. CT scanning with radiocontrast enhancement could be performed; however, it is less helpful than MRI for small lesions or tumors in the posterior fossa. The characteristic appearance of meningiomas on MRI or CT scanning is virtually diagnostic, ie, a lesion in a typical site (parasagittal and sylvian regions, olfactory groove, sphenoidal ridge, tuberculum sellae) that appears as a homogeneous area of increased density in noncontrast scans and enhances uniformly with contrast. Additional MRI sequences that may be helpful in differentiating gliomas from other intracranial pathology include perfusion imaging, magnetic resonance spectroscopy, and diffusion-weighted imaging, although none are specific enough to obviate the need for tissue

sampling. Arteriography is largely reserved for presurgical embolization of highly vascular tumors. In patients with normal hormone levels and an intrasellar mass, angiography is sometimes necessary to distinguish with confidence between a pituitary adenoma and an arterial aneurysm.

C. Laboratory and Other Studies

When glial neoplasms are suspected, biopsy is necessary for definitive histologic diagnosis and molecular analysis. The World Health Organization classifies glial tumors by both histology and genetic characteristics. Lumbar puncture is rarely necessary; the findings are seldom diagnostic, and the procedure carries the risk of causing a herniation syndrome. Suspected intracranial germ cell tumors are an exception. If lumbar puncture can be performed safely, cytology and determination of alpha-fetoprotein and beta-human chorionic gonadotropin should be performed in cerebrospinal fluid; tumor markers should be examined in serum as well.

Treatment

Treatment depends on the type and site of the tumor (Table 24–4) and the condition of the patient. Some benign tumors, especially meningiomas discovered incidentally during brain imaging for another purpose, may be monitored with serial annual imaging. For symptomatic tumors, complete surgical removal may be possible if the tumor is extra-axial (eg, meningioma, acoustic neuroma) or is not in a critical or inaccessible region of the brain (eg, cerebellar hemangioblastoma). Surgery also permits the diagnosis to be verified and may be beneficial in reducing intracranial pressure and relieving symptoms even if the neoplasm cannot be completely removed. Clinical deficits are sometimes due in part to obstructive hydrocephalus, in which case simple surgical shunting procedures often produce dramatic benefit. In patients with malignant gliomas, survival correlates to the extent of initial resection.

Radiation therapy increases median survival rates regardless of any preceding surgery, and its combination with chemotherapy provides additional benefit. Indications for irradiation in the treatment of patients with other primary intracranial neoplasms depend on tumor type and accessibility and the feasibility of complete surgical removal. Long-term neurocognitive deficits may complicate radiation therapy. Temozolomide is a commonly used oral and intravenous chemotherapeutic for gliomas. In patients with glioblastoma with methylated methylguanine-DNA methyltransferase (MGMT) promoter, combination therapy with lomustine and temozolomide improved median survival from 31 to 48 months in a randomized controlled trial. The addition of low-intensity, 200 kHz frequency alternating electric fields (tumor treatment fields) delivered extracranially at least 18 hours daily, improves progression-free survival by 2.7 months and median survival by 4.9 months compared to temozolomide alone in glioblastoma. Bevacizumab is approved in the United States but not in Europe for use in recurrent high-grade glioma. Combination therapy with procarbazine, lomustine, and vincristine improves median survival when given with radiation to

patients with isocitrate dehydrogenase-mutant astrocytoma and isocitrate dehydrogenase-mutant, p1/19q co-deleted oligodendrogloma.

Corticosteroids help reduce cerebral edema and are usually started before surgery. Herniation is treated with intravenous dexamethasone (10–20 mg as a bolus, followed by 4 mg every 6 hours) and intravenous mannitol (20% solution given in a dose of 1.5 g/kg over about 30 minutes).

Anticonvulsants are also commonly administered in standard doses (see Table 24–2), but are not indicated for prophylaxis in patients who have no history of seizures. For those patients with difficult to treat symptoms or those needing help with advance care planning, specialty palliative care consultation is appropriate (see Chapter 5).

► When to Refer

All patients should be referred.

► When to Admit

- All patients with increased intracranial pressure.
- All patients requiring biopsy, surgical treatment, or shunting procedures.

Bell EH et al. Comprehensive genomic analysis in NRG oncology/RTG 9802: a phase III trial of radiation versus radiation plus procarbazine, lomustine (CCNU), and vincristine in high-risk low-grade glioma. *J Clin Oncol.* 2020;38:3407. [PMID: 32706640]

Desjardins A et al. Recurrent glioblastoma treated with recombinant poliovirus. *N Engl J Med.* 2018;379:150. [PMID: 29943666]

Herrlinger U et al; Neurooncology Working Group of the German Cancer Society. Lomustine-temozolamide combination therapy versus standard temozolamide therapy in patients with newly diagnosed glioblastoma with methylated MGMT promoter (CeTeG/NOA-09): a randomised, open-label, phase 3 trial. *Lancet.* 2019;393:678. [PMID: 30782343]

2. Metastatic Intracranial Tumors

A. Cerebral Metastases

Metastatic brain tumors present in the same way as other cerebral neoplasms, ie, with increased intracranial pressure, with focal or diffuse disturbance of cerebral function, or with both of these manifestations. Indeed, in patients with a single cerebral lesion, the metastatic nature of the lesion may become evident only on histopathologic examination. In other patients, there is evidence of widespread metastatic disease, or an isolated cerebral metastasis develops during treatment of the primary neoplasm.

The most common source of intracranial metastasis is carcinoma of the lung; other primary sites are the breast, kidney, skin (melanoma), and gastrointestinal tract. Most cerebral metastases are located supratentorially. Laboratory and radiologic studies used to evaluate patients with metastases are those described for primary neoplasms. They include MRI and CT scanning performed both with and without contrast. Lumbar puncture is necessary only in patients with suspected carcinomatous meningitis. In patients with verified cerebral metastasis from an unknown

primary, investigation is guided by symptoms and signs. In women, mammography is indicated; in men under 50, germ cell origin is sought.

Treatment of brain metastases is rapidly evolving and a multidisciplinary approach between neurosurgery, radiation oncology, and oncology is necessary. In patients with only a single, surgically accessible cerebral metastasis who are otherwise well (ie, a high level of functioning and little or no evidence of extracranial disease), it may be possible to remove the lesion and then treat with irradiation; the latter may also be selected as the sole treatment. Systemic immunotherapy may also be an acceptable initial option in select cases. In patients with multiple metastases or widespread systemic disease, stereotactic radiosurgery, whole-brain radiotherapy, or both may help in some instances; systemic chemotherapy or immunotherapy may be options in others, but in many, treatment is palliative only.

Fuentes R et al. Surgery versus stereotactic radiotherapy for people with single or solitary brain metastasis. Cochrane Database Syst Rev. 2018;8:CD012086. [PMID: 30125049]

Tsao MN et al. Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases. Cochrane Database Syst Rev. 2018;1:CD003869. [PMID: 29365347]

B. Leptomeningeal Metastases (Carcinomatous Meningitis)

The neoplasms metastasizing most commonly to the leptomeninges are carcinoma of the breast and lung, lymphomas, and leukemia (see Chapter 39). Leptomeningeal metastases lead to multifocal neurologic deficits, which may be associated with infiltration of cranial and spinal nerve roots, direct invasion of the brain or spinal cord, obstructive or communicating hydrocephalus, or some combination of these factors.

The diagnosis is confirmed by examination of the cerebrospinal fluid. Findings may include elevated cerebrospinal fluid pressure, pleocytosis, increased protein concentration, and decreased glucose concentration. Cytologic studies may indicate that malignant cells are present; if not, lumbar puncture should be repeated at least twice to obtain further samples for analysis.

CT scans showing contrast enhancement in the basal cisterns or showing hydrocephalus without any evidence of a mass lesion support the diagnosis. Gadolinium-enhanced MRI is more sensitive and frequently shows enhancing foci in the leptomeninges. Myelography may show deposits on multiple nerve roots.

Treatment is by irradiation to symptomatic areas, combined with intrathecal chemotherapy in select patients. The long-term prognosis is poor—only about 10% of patients survive for 1 year—and palliative care is therefore important (see Chapter 5).

3. Intracranial Mass Lesions in Patients with AIDS

Primary cerebral lymphoma is a common complication in patients with AIDS. This leads to disturbances in cognition or consciousness, focal motor or sensory deficits,

aphasia, seizures, and cranial neuropathies. Similar clinical disturbances may result from **cerebral toxoplasmosis**, which is also a common complication in patients with AIDS (see Chapters 31 and 35). Neither CT nor MRI findings distinguish these two disorders and serologic tests for toxoplasmosis are unreliable in AIDS patients. *Toxoplasma gondii* DNA detected by polymerase chain reaction in the spinal fluid is specific but not sensitive for toxoplasmosis, and the finding of Epstein-Barr virus DNA suggests lymphoma but is not specific enough to initiate treatment. Accordingly, for neurologically stable patients, a trial of treatment for toxoplasmosis with pyrimethamine and sulfadiazine is recommended for 3 weeks; the imaging studies are then repeated, and if any lesion has improved, the regimen is continued indefinitely. If any lesion does not improve, cerebral biopsy is necessary (see also Chapter 31). Primary cerebral lymphoma in patients with AIDS is treated with corticosteroids, high-dose methotrexate, and antiretroviral therapy. Rituximab may be used in some patients. Whole-brain irradiation may not be necessary.

Cryptococcal meningitis is a common opportunistic infection in patients with AIDS. Clinically, it may resemble cerebral toxoplasmosis or lymphoma, but cranial CT scans are usually normal (see Chapter 36).

4. Primary & Metastatic Spinal Tumors

Approximately 10% of spinal tumors are intramedullary. Ependymoma is the most common type of intramedullary tumor; the remainder are other types of glioma. Extramedullary tumors may be extradural or intradural in location. Among the primary extramedullary tumors, neurofibromas and meningiomas are relatively common, benign, and may be intradural or extradural. Carcinomatous metastases, lymphomatous or leukemic deposits, and myeloma are usually extradural; in the case of metastases, the prostate, breast, lung, and kidney are common primary sites.

Tumors may lead to spinal cord dysfunction by direct compression, by ischemia secondary to arterial or venous obstruction and, in the case of intramedullary lesions, by invasive infiltration.

► Clinical Findings

A. Symptoms and Signs

Symptoms usually develop insidiously. Pain is often conspicuous with extradural lesions; is characteristically aggravated by coughing or straining; may be radicular, localized to the back, or felt diffusely in an extremity; and may be accompanied by motor deficits, paresthesias, or numbness, especially in the legs. Bladder, bowel, and sexual dysfunction may occur. When sphincter disturbances occur, they are usually particularly disabling. Pain, however, often precedes specific neurologic symptoms from epidural metastases.

Examination may reveal localized spinal tenderness. A segmental lower motor neuron deficit or dermatomal sensory changes (or both) are sometimes found at the level of the lesion, while an upper motor neuron deficit and sensory disturbance are found below it.

B. Imaging

MRI with contrast or CT myelography is used to identify and localize the lesion. The combination of known tumor elsewhere in the body, back pain, and either abnormal plain films of the spine or neurologic signs of cord compression is an indication to perform this on an *urgent* basis.

C. Laboratory Findings

The cerebrospinal fluid is often xanthochromic and contains a greatly increased protein concentration with normal cell content and glucose concentration.

D. Treatment

Intramedullary tumors are treated by decompression and surgical excision (when feasible) and by irradiation. The prognosis depends on the cause and severity of cord compression before it is relieved.

Treatment of epidural spinal metastases consists of surgical decompression, radiation, or both. Dexamethasone is also given in a high dosage (eg, 10–96 mg once intravenously, followed by 4–25 mg four times daily for 3 days orally or intravenously, followed by rapid tapering of the dosage, depending on initial dose and response) to reduce cord swelling and relieve pain. Radiation alone is often all that is required in patients with radiosensitive tumors. Surgical decompression is reserved for patients with tumors that are unresponsive to irradiation or who have previously been irradiated, for those with spinal instability, and for patients in whom there is some uncertainty about the diagnosis. The long-term outlook is poor, but treatment may at least delay the onset of major disability.

Lawton AJ et al. Assessment and management of patients with metastatic spinal cord compression: a multidisciplinary review. *J Clin Oncol*. 2019;37:61. [PMID: 30395488]

5. Brain Abscess



ESSENTIALS OF DIAGNOSIS

- ▶ Signs of expanding intracranial mass.
- ▶ Signs of primary infection or congenital heart disease are sometimes present.
- ▶ Fever may be absent.

E. General Considerations

Brain abscess presents as an intracranial space-occupying lesion and arises as a sequela of disease of the ear or nose, may be a complication of infection elsewhere in the body, or may result from infection introduced intracranially by trauma or surgical procedures. The most common infective organisms are streptococci, staphylococci, and anaerobes; mixed infections also occur.

Clinical Findings

A. Symptoms and Signs

Headache, drowsiness, inattention, confusion, and seizures are early symptoms, followed by signs of increasing intracranial pressure and then a focal neurologic deficit. There may be little or no systemic evidence of infection.

B. Imaging and Other Investigations

A CT scan of the head characteristically shows an area of contrast enhancement surrounding a low-density core. Similar abnormalities may be found in patients with metastatic neoplasms. MRI findings often permit earlier recognition of focal cerebritis or an abscess. Stereotactic needle aspiration may enable a specific etiologic organism to be identified. Examination of the cerebrospinal fluid does not help in diagnosis and may precipitate a herniation syndrome. Peripheral leukocytosis is sometimes present.

D. Treatment

Treatment consists of intravenous antibiotics combined with surgical drainage (aspiration or excision), if necessary, to reduce the mass effect or sometimes to establish the diagnosis. Abscesses smaller than 2 cm can often be cured medically. Broad-spectrum antibiotics, selected based on risk factors and likely organisms, are used if the infecting organism is unknown (see Chapter 33). An initial empiric multi-antibiotic regimen typically includes ceftriaxone (2 g intravenously every 12 hours), metronidazole (15 mg/kg intravenous loading dose, followed by 7.5 mg/kg intravenously every 6 hours), and vancomycin (1 g intravenously every 12 hours). The regimen is altered once culture and sensitivity data are available. Antimicrobial treatment is usually continued parenterally for 6–8 weeks and is followed by oral treatment for certain infections, such as nocardiosis, actinomycosis, fungal infections, and tuberculosis. The patient should be monitored by serial CT scans or MRI every 2 weeks and at deterioration. Dexamethasone (4–25 mg four times daily intravenously or orally, depending on severity, followed by tapering of dose, depending on response) may reduce any associated edema, but intravenous mannitol is sometimes required.

Chow F. Brain and spinal epidural abscess. *Continuum (Minneapolis Minn)*. 2018;24:1327. [PMID: 30273242]

NONMETASTATIC NEUROLOGIC COMPLICATIONS OF MALIGNANT DISEASE

A variety of nonmetastatic neurologic complications of malignant disease can be recognized. **Metabolic encephalopathy** due to electrolyte abnormalities, infections, drug overdose, or the failure of some vital organ may be reflected by drowsiness, lethargy, restlessness, insomnia, agitation, confusion, stupor, or coma. The mental changes are usually associated with tremor, asterixis, and multifocal myoclonus. The electroencephalogram is generally diffusely slowed. Laboratory studies are necessary to detect the cause of the encephalopathy, which must then be treated appropriately.

Immune suppression resulting from either the malignant disease or its treatment (eg, by chemotherapy) predisposes patients to brain abscess, progressive multifocal leukoencephalopathy, meningitis, herpes zoster infection, and other opportunistic infectious diseases. Moreover, an overt or occult cerebrospinal fluid fistula, as occurs with some tumors, may also increase the risk of infection. MRI or CT scanning aids in the early recognition of a brain abscess, but metastatic brain tumors may have a similar appearance. Examination of the cerebrospinal fluid is essential in the evaluation of patients with meningitis and encephalitis but is of no help in the diagnosis of brain abscess.

Cerebrovascular disorders that cause neurologic complications in patients with systemic cancer include nonbacterial thrombotic endocarditis and septic embolization. Cerebral, subarachnoid, or subdural hemorrhages may occur in patients with myelogenous leukemia and may be found in association with metastatic tumors, especially melanoma. Spinal subdural hemorrhage sometimes occurs after lumbar puncture in patients with marked thrombocytopenia.

Disseminated intravascular coagulation occurs most commonly in patients with acute promyelocytic leukemia or with some adenocarcinomas and is characterized by a fluctuating encephalopathy, often with associated seizures, that frequently progresses to coma or death. There may be few accompanying neurologic signs. **Venous sinus thrombosis**, which usually presents with convulsions and headaches, may also occur in patients with leukemia or lymphoma. Examination commonly reveals papilledema and focal or diffuse neurologic signs. Anticonvulsants, anticoagulants, and medications to lower the intracranial pressure may be of value.

Autoimmune paraneoplastic disorders occur when the immune system reacts against neuronal antigens expressed by tumor cells. The clinical manifestations depend on the autoantibody. Symptoms may precede those due to the neoplasm itself. Several distinct syndromes are common, each associated with specific antibodies and tumors (Table 24–5). Identification of an antibody is not always possible in a suspected autoimmune paraneoplastic condition, and a search for an underlying neoplasm should be undertaken. Treatment of the neoplasm offers the best hope for stabilization or improvement of the neurologic symptoms, which often are not completely reversible. Specific treatment of the antibody-mediated symptoms by intravenous immunoglobulin (IVIG) administration, plasmapheresis, corticosteroids, or other immunosuppressive regimens is frequently attempted despite limited evidence of efficacy. Many of the disorders listed in Table 24–5 can occur either as paraneoplastic phenomena or in isolation; when they occur in the absence of a tumor, the response to immunotherapy is typically more favorable.

Autoimmune disorders may also be triggered as a result of cancer immunotherapy; encephalitis, meningitis, transverse myelitis, acute and chronic inflammatory demyelinating polyneuropathy, autonomic neuropathy, myasthenia gravis, and myositis have all been described.

Rosenfeld MR et al. Paraneoplastic neurologic syndromes. *Neurol Clin*. 2018;36:675. [PMID: 30072076]

IDIOPATHIC INTRACRANIAL HYPERTENSION (Pseudotumor Cerebri)



ESSENTIALS OF DIAGNOSIS

- ▶ Headache, worse on straining.
- ▶ Visual obscurations or diplopia may occur.
- ▶ Examination reveals papilledema.
- ▶ Abducens palsy is commonly present.

General Considerations

There are many causes of this disorder. Thrombosis of the transverse venous sinus as a complication of otitis media or chronic mastoiditis is one cause, and sagittal sinus thrombosis may lead to a clinically similar picture. Other causes include chronic pulmonary disease, systemic lupus erythematosus, uremia, endocrine disturbances such as hypoparathyroidism, hypothyroidism, or Addison disease, vitamin A toxicity, and the use of tetracycline or oral contraceptives. Cases have also followed withdrawal of corticosteroids after long-term use. In most instances, however, no specific cause can be found, and the disorder remits spontaneously after several months. This idiopathic variety occurs most commonly among overweight women aged 20–44. In all cases, screening for a space-occupying lesion of the brain is important.

Clinical Findings

A. Symptoms and Signs

Symptoms consist of headache, diplopia, and other visual disturbances due to papilledema and abducens nerve dysfunction. Pulse-synchronous tinnitus may also occur. Examination reveals papilledema and some enlargement of the blind spots, but patients otherwise look well.

B. Imaging

Investigations reveal no evidence of a space-occupying lesion. CT or MRI shows small or normal ventricles and an empty sella turcica. MR venography is important in screening for thrombosis of the intracranial venous sinuses. In some cases, stenosis of one or more of the venous sinuses will be observed.

C. Laboratory Findings

Lumbar puncture is necessary to confirm the presence of intracranial hypertension, but the cerebrospinal fluid is normal. Laboratory studies help exclude some of the other causes mentioned earlier.

Treatment

Untreated intracranial hypertension sometimes leads to secondary optic atrophy and permanent visual loss. Acetazolamide (250–500 mg orally three times daily, increasing slowly to a maintenance dose of up to 4000 mg daily,

Table 24-5. Autoimmune paraneoplastic disorders and their associated antibodies and tumors (listed in alphabetical order).

Syndrome	Clinical Features	Associated Antibodies	Typical Associated Tumors
Anti-NMDA receptor-associated encephalitis	Paranoia, delusions, behavioral disturbance, seizure, orofacial dyskinesias, athetosis, dysautonomia, hypoventilation	NMDA receptor ¹	Ovarian teratoma, lung, breast, ovary, testicle
Autoimmune necrotizing myopathy	Weakness	SRP ¹ HMGCR ¹	Lung, breast, gastrointestinal, bladder
Autonomic neuropathy	Postural hypotension, gastroparesis	Hu, ganglionic AChR ¹	
Cerebellar degeneration	Ataxia, dysarthria, nystagmus	GAD65, ¹ KLHL11, mGluR1, ¹ NIF, ¹ Ri, Tr, VGCC, ¹ Yo	Lung, breast, thymus, ovary, testicle, Hodgkin lymphoma
Dermatomyositis	Weakness, heliotrope skin rash	TIF-1 gamma	Lung, breast, ovary, gastrointestinal, lymphoma
Lambert-Eaton myasthenic syndrome	Fatiguable weakness, ptosis, diplopia, dry mouth, constipation	VGCC ¹	Lung
Limbic encephalitis/encephalomyelitis	Short-term memory loss, hallucinations, seizures, behavioral disturbance, encephalopathy	AMPA receptor, ¹ Caspr2, ¹ CV2/CRMP5, DPPX, ¹ GABA _A receptor, ¹ GABA _B receptor, ¹ GAD65, ¹ GFAP, ¹ Hu, LGI1, ¹ Ma2, mGluR5, ¹ NIF, ¹ thyroglobulin ¹ /thyroperoxidase ¹	Lung, breast, thymus, ovary, testicle, Hodgkin lymphoma
Myasthenia gravis	Fatiguable weakness, ptosis, diplopia	AChR, ¹ LRP4, ¹ MuSK ¹	Thymus
Myelitis	Paraparesis, bowel and bladder dysfunction; sensory level	Amphiphysin, ¹ aquaporin 4, ¹ CRMP-5, GFAP, ¹ Hu, MOG, ¹ Yo	Lung, breast, lymphoma, leukemia, thyroid, renal
Opsoclonus/myoclonus	Erratic, conjugate saccadic eye movements and limb myoclonus	Ri	Lung, breast, ovary, testicle, neuroblastoma (children)
Retinopathy	Vision loss	Anti-recoverin, anti-retinal bipolar cell	Small cell lung, melanoma
Sensorimotor neuropathy	Numbness with or without weakness; may be mild and chronic or acute and severe	Hu, MAG	
Sensory neuronopathy	Pain, numbness, sensory ataxia, hearing loss	Hu	Small cell lung
Stiff person syndrome	Co-contraction of antagonist and agonist muscles	Amphiphysin, ¹ GAD65, ¹ GlyR ¹	Small cell lung, breast, thymus, lymphoma

¹Can occur in absence of tumor.

AChR, acetylcholine receptor; AMPA, alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid; Caspr2, contactin associated protein-like 2; CRMP, collapsin response-mediator protein; DPPX, dipeptidyl-peptidase-like protein-6; GABA, gamma-aminobutyric acid; GAD, glutamic acid decarboxylase; GFAP, glial fibrillary acidic protein; GlyR, glycine receptor; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; KLHL11, kelch-like protein 11; LGI1, leucine rich glioma inactivated; LRP4, low-density lipoprotein receptor-related protein 4; mGluR, metabotropic glutamate receptor; MAG, myelin-associated glycoprotein; MOG, myelin oligodendrocyte glycoprotein; MuSK, Muscle-specific tyrosine kinase; NIF, neuronal intermediate filament; NMDA, N-methyl-D-aspartate; SRP, signal recognition particle; TIF-1, human transcription intermediary factor-1; VGCC, voltage-gated calcium channel.

divided two to four times daily) reduces formation of cerebrospinal fluid. Like acetazolamide, the antiepileptic medication topiramate (Table 24-2) is a carbonic anhydrase inhibitor and was shown to be similarly effective in an open label study; topiramate has the added benefit of causing weight loss. Furosemide (20–40 mg daily) may be helpful as adjunct therapy. Corticosteroids (eg, prednisone 60–80 mg daily) are sometimes prescribed, but side effects and the risk of relapse on withdrawal have discouraged

their use. Obese patients should be advised to lose weight. Repeated lumbar puncture to lower the intracranial pressure by removal of cerebrospinal fluid is effective as a temporizing measure, but pharmacologic approaches to treatment provide better long-term relief. Treatment is monitored by checking visual acuity and visual fields, funduscopic appearance, and pressure of the cerebrospinal fluid. The disorder may worsen after a period of stability, indicating the need for long-term follow-up.

If medical treatment fails to control the intracranial pressure, surgical placement of a lumboperitoneal or ventriculoperitoneal shunt or optic nerve sheath fenestration should be undertaken to preserve vision. Venous sinus stenting is an increasingly accepted therapeutic option for dural venous sinus stenosis.

In addition to the above measures, any specific cause of intracranial hypertension requires appropriate treatment. Thus, hormone therapy should be initiated if there is an underlying endocrine disturbance. Discontinuing the use of tetracycline, oral contraceptives, or vitamin A will allow for resolution of intracranial hypertension due to these agents. If corticosteroid withdrawal is responsible, the medication should be reintroduced and then tapered more gradually.

► When to Refer

All patients should be referred.

► When to Admit

All patients with worsening vision requiring shunt placement or optic nerve sheath fenestration should be hospitalized.

Kalyvas A et al. A systematic review of surgical treatments of idiopathic intracranial hypertension (IIH). *Neurosurg Rev*. 2021;44:773. [PMID: 32335853]

Madriz Peralta G et al. An update of idiopathic intracranial hypertension. *Curr Opin Ophthalmol*. 2018;29:495. [PMID: 30169466]

rapamycin (mTOR) inhibitor, is approved in the United States and Europe for medically refractory epilepsy and subependymal giant cell astrocytomas due to tuberous sclerosis.

2. Neurofibromatosis

Neurofibromatosis may occur either sporadically or on a familial basis with autosomal dominant inheritance. Two distinct forms are recognized: **Type 1 (Recklinghausen disease)** is characterized by multiple hyperpigmented macules, Lisch nodules, and neurofibromas, and results from mutations in the *NF1* gene on chromosome 17. **Type 2** is characterized by bilateral eighth nerve tumors, often accompanied by other intracranial or intraspinal tumors, and is associated with mutations in the *NF2* (merlin) gene on chromosome 22.

Neurologic presentation is usually with symptoms and signs of tumor. Multiple neurofibromas characteristically are present and may involve spinal or cranial nerves, especially the eighth nerve. Examination of the superficial cutaneous nerves usually reveals palpable mobile nodules. In some cases, there is marked overgrowth of subcutaneous tissues (plexiform neurofibromas), sometimes with an underlying bony abnormality. Associated cutaneous lesions include axillary freckling and patches of cutaneous pigmentation (**café au lait spots**). Malignant degeneration of neurofibromas occasionally occurs and may lead to peripheral sarcomas. Meningiomas, gliomas (especially optic nerve gliomas), bone cysts, pheochromocytomas, scoliosis, and obstructive hydrocephalus may also occur. Selumetinib (25 mg/m² orally twice daily), a mitogen-activated protein kinase inhibitor, causes plexiform neurofibromas to shrink by at least 20% in two-thirds of patients and is approved by the FDA for treatment of inoperable plexiform neurofibromas in children 2 years of age and older. Studies in adults are ongoing.

3. Sturge-Weber Syndrome

Sturge-Weber syndrome consists of a congenital, usually unilateral, cutaneous capillary angioma involving the upper face, leptomeningeal angiomas, and, in many patients, choroidal angioma. It has no sex predilection and usually occurs sporadically. The cutaneous angioma sometimes has a more extensive distribution over the head and neck and is often quite disfiguring, especially if there is associated overgrowth of connective tissue. Focal or generalized seizures are the usual neurologic presentation and may commence at any age. There may be contralateral homonymous hemianopia, hemiparesis and hemisensory disturbance, ipsilateral glaucoma, and mental subnormality. Skull radiographs taken after the first 2 years of life usually reveal gyral ("tramline") intracranial calcification, especially in the parieto-occipital region, due to mineral deposition in the cortex beneath the intracranial angioma.

Treatment is aimed at controlling seizures pharmacologically (Table 24-2), but surgical treatment may be necessary. Ophthalmologic advice should be sought concerning the management of choroidal angioma and of increased intraocular pressure.

SELECTED NEUROCUTANEOUS DISEASES

Because the nervous system develops from the epithelial layer of the embryo, a number of congenital diseases include both neurologic and cutaneous manifestations. Among these disorders, three are discussed below, and von Hippel-Lindau disease is discussed in Chapter 26.

1. Tuberous Sclerosis

Tuberous sclerosis may occur sporadically or on a familial basis with autosomal dominant inheritance. Neurologic presentation is with seizures and progressive psychomotor retardation beginning in early childhood. The cutaneous abnormality adenoma sebaceum becomes manifest usually between 5 and 10 years of age and typically consists of reddened nodules on the face (cheeks, nasolabial folds, sides of the nose, and chin) and sometimes on the forehead and neck. Other typical cutaneous lesions include subungual fibromas, shagreen patches (leathery plaques of subepidermal fibrosis, situated usually on the trunk), and leaf-shaped hypopigmented spots. Associated abnormalities include retinal lesions and tumors, benign rhabdomyomas of the heart, lung cysts, benign tumors in the viscera, and bone cysts.

The disease is slowly progressive and leads to increasing mental deterioration. Anticonvulsants are indicated to control seizures. Everolimus, a mammalian target of

MOVEMENT DISORDERS

1. Essential (Familial) Tremor



ESSENTIALS OF DIAGNOSIS

- ▶ Postural tremor of hands, head, or voice.
- ▶ Family history common.
- ▶ May improve temporarily with alcohol.
- ▶ No abnormal findings other than tremor.

► General Considerations

The cause of essential tremor is uncertain, but it is sometimes inherited in an autosomal dominant manner.

► Clinical Findings

Tremor may begin at any age and is enhanced by emotional stress. The tremor usually involves one or both hands, the head, or the hands and head, while the legs tend to be spared. The tremor is not present at rest, but emerges with action. Examination reveals no other abnormalities. Ingestion of a small quantity of alcohol commonly provides remarkable but short-lived relief by an unknown mechanism.

The tremor typically becomes more conspicuous with time. Occasionally, it interferes with manual skills and leads to impairment of handwriting. Speech may also be affected if the laryngeal muscles are involved.

► Treatment

Treatment is often unnecessary. When it is required because of disability, propranolol (60–240 mg daily orally) may be helpful. Long-term therapy is typical; however, intermittent therapy is sometimes useful in patients whose tremor becomes exacerbated in specific predictable situations. Primidone may be helpful when propranolol is ineffective, but patients with essential tremor are often very sensitive to it. Therefore, the starting dose is 50 mg daily orally, and the daily dose is increased by 50 mg every 2 weeks depending on the patient's response; a maintenance dose of 125 mg three times daily orally is commonly effective. Occasional patients do not respond to these measures but are helped by alprazolam (up to 3 mg daily orally in divided doses), topiramate (titrated up to a dose of 400 mg daily orally in divided doses over about 8 weeks), or gabapentin (1800 mg daily orally in divided doses). Botulinum toxin A may reduce tremor, but adverse effects include dose-dependent weakness of the injected muscles.

Disabling tremor unresponsive to medical treatment may be helped by high-frequency thalamic stimulation ("deep brain stimulation") on one or both sides, according to the laterality of symptoms. Focused transcranial ultrasound thalamotomy using MRI guidance is also effective, as is stereotactic radiosurgery for unilateral upper extremity tremor.

► When to Refer

- When refractory to first-line treatment with propranolol or primidone.
- When additional neurologic signs are present (ie, parkinsonism).

► When to Admit

Patients requiring surgical treatment (deep brain stimulator placement) should be hospitalized.

Haubenberger D et al. Essential tremor. N Engl J Med. 2018;378:1802. [PMID: 29742376]

2. Parkinson Disease



ESSENTIALS OF DIAGNOSIS

- ▶ Any combination of tremor, rigidity, bradykinesia, and progressive postural instability ("parkinsonism").
- ▶ Cognitive impairment is sometimes prominent.

► General Considerations

Parkinsonism is a relatively common disorder that occurs in all ethnic groups, with an approximately equal sex distribution. The most common variety, idiopathic Parkinson disease, begins most often between 45 and 65 years of age and is a progressive disease.

► Etiology

Parkinsonism may rarely occur on a familial basis, and the parkinsonian phenotype may result from mutations of several different genes. Postencephalitic parkinsonism is becoming increasingly rare. Exposure to certain toxins (eg, manganese dust, carbon disulfide) and severe carbon monoxide poisoning may lead to parkinsonism. Reversible parkinsonism may develop in patients receiving neuroleptic medications (see Chapter 25), reserpine, or metoclopramide. Only rarely is hemiparkinsonism the presenting feature of a progressive space-occupying lesion.

In idiopathic Parkinson disease, dopamine depletion due to degeneration of the dopaminergic nigrostriatal system leads to an imbalance of dopamine and acetylcholine, which are neurotransmitters normally present in the corpus striatum. Treatment of the motor disturbance is directed at redressing this imbalance by blocking the effect of acetylcholine with anticholinergic medications or by the administration of levodopa, the precursor of dopamine. Prior use of ibuprofen is associated with a *decreased* risk of developing Parkinson disease; age, family history, male sex, ongoing herbicide/pesticide exposure, and significant prior head trauma are risk factors.

► Clinical Findings

Tremor, rigidity, bradykinesia, and postural instability are the cardinal motor features of parkinsonism and may

be present in any combination. Nonmotor manifestations include affective disorders (depression, anxiety, and apathy), psychosis, cognitive changes, fatigue, sleep disorders, anosmia, autonomic disturbances, sensory complaints or pain, and seborrheic dermatitis. Dementia or mild cognitive impairment will eventually develop in many patients.

The tremor of about four to six cycles per second is *most conspicuous at rest*, is enhanced by emotional stress, and is often less severe during voluntary activity. Although it may ultimately be present in all limbs, the tremor is commonly confined to one limb or to the limbs on one side for months or years before it becomes more generalized. In some patients, tremor is absent.

Rigidity (an increase in resistance to passive movement) is responsible for the characteristically flexed posture seen in many patients, but the most disabling symptoms of parkinsonism are due to bradykinesia, manifested as a slowness of voluntary movement and a reduction in automatic movements such as swinging of the arms while walking. Curiously, however, effective voluntary activity may briefly be regained during an emergency (eg, the patient is able to leap aside to avoid an oncoming motor vehicle).

Clinical diagnosis of the well-developed syndrome is usually simple. The patient has a relatively immobile face with widened palpebral fissures, infrequent blinking, and a fixity of facial expression. Seborrhea of the scalp and face is common. There is often mild blepharoclonus, and a tremor may be present about the mouth and lips. Repetitive tapping (about twice per second) over the bridge of the nose produces a sustained blink response (**Myerson sign**). Other findings may include saliva drooling from the mouth, perhaps due to impairment of swallowing; soft and poorly modulated voice; a variable rest tremor and rigidity in some or all of the limbs; slowness of voluntary movements; impairment of fine or rapidly alternating movements; and micrographia. There is typically no muscle weakness (provided that sufficient time is allowed for power to be developed) and no alteration in the tendon reflexes or plantar responses. It is difficult for the patient to arise from a sitting position and begin walking. The gait itself is characterized by small shuffling steps and a loss of the normal automatic arm swing; there may be unsteadiness on turning, difficulty in stopping, and a tendency to fall.

Differential Diagnosis

Diagnostic problems may occur in mild cases, especially if tremor is minimal or absent. For example, mild hypokinesia or slight tremor is commonly attributed to old age. Depression, with its associated expressionless face, poorly modulated voice, and reduction in voluntary activity, can be difficult to distinguish from mild parkinsonism, especially since the two disorders may coexist. The family history, the character of the tremor, and lack of other neurologic signs should distinguish essential tremor from parkinsonism. Wilson disease can be distinguished by its early age at onset, the presence of other abnormal movements, Kayser-Fleischer rings, and chronic hepatitis, and by increased concentrations of copper in the tissues. Huntington disease presenting with rigidity and bradykinesia may be mistaken

for parkinsonism unless the family history and accompanying dementia are recognized. In multisystem atrophy (previously called the Shy-Drager syndrome), autonomic insufficiency (leading to postural hypotension, anhidrosis, disturbances of sphincter control, erectile dysfunction, etc) may be accompanied by parkinsonism, pyramidal deficits, lower motor neuron signs, or cerebellar dysfunction. In progressive supranuclear palsy, bradykinesia and rigidity are accompanied by a supranuclear disorder of eye movements, pseudobulbar palsy, pseudo-emotional lability (pseudobulbar affect), and axial dystonia. Creutzfeldt-Jakob disease may be accompanied by features of parkinsonism, but progression is rapid, dementia is usual, myoclonic jerking is common, ataxia and pyramidal signs may be conspicuous, and the MRI and electroencephalographic findings are usually characteristic. In corticobasal degeneration, asymmetric parkinsonism is accompanied by conspicuous signs of cortical dysfunction (eg, apraxia, sensory inattention, dementia, aphasia). Diffuse Lewy body disease is characterized by prominent visual hallucinations and cognitive impairment that begin before or within 1 year of onset of the motor features of parkinsonism.

Treatment

Treatment is symptomatic. There is great interest in developing disease-modifying therapies, but trials of several putative neuroprotective agents have shown no benefit. Trials of various gene therapies have shown limited or no benefit.

A. Medical Measures

Medication is not required early in the course of Parkinson disease, but the nature of the disorder and the availability of medical treatment for use when necessary should be discussed with the patient.

1. Amantadine—Patients with mild symptoms but no disability may be helped by amantadine (100 mg orally two to three times daily [immediate release] or once daily [extended release]). This medication improves all of the clinical features of parkinsonism, but its mode of action is unclear. Side effects are uncommon but may include restlessness, confusion, depression, skin rashes, edema, nausea, constipation, anorexia, postural hypotension, and disturbances of cardiac rhythm. It also ameliorates dyskinesias resulting from long-term levodopa therapy.

2. Levodopa—Levodopa, which is converted in the body to dopamine, improves all of the major features of parkinsonism, including bradykinesia, but *does not stop progression* of the disorder. The most common early side effects of levodopa are nausea, vomiting, and hypotension, but cardiac arrhythmias may also occur. Dyskinesias, restlessness, confusion, and other behavioral changes tend to occur somewhat later and become more common with time. **Levodopa-induced dyskinesias** may take any conceivable form, including chorea, athetosis, dystonia, tremor, tics, and myoclonus. An even later complication is the **wearing off effect** or the **on-off phenomenon**, in which abrupt but transient fluctuations in the severity of parkinsonism occur

unpredictably but frequently during the day. The “off” period of marked bradykinesia has been shown to relate in some instances to falling plasma levels of levodopa. During the “on” phase, dyskinesias are often conspicuous but mobility is increased. However, such response fluctuations may relate to advancing disease rather than to levodopa therapy itself.

Carbidopa, which inhibits the enzyme responsible for the breakdown of levodopa to dopamine, does not cross the blood-brain barrier. When levodopa is given in combination with carbidopa, the extracerebral breakdown of levodopa is diminished. This reduces the amount of levodopa required daily for beneficial effects, and it lowers the incidence of nausea, vomiting, hypotension, and cardiac irregularities. Such a combination does not prevent the development of response fluctuations and the incidence of other side effects (dyskinesias or psychiatric complications) may actually be increased.

Sinemet, a commercially available preparation that contains carbidopa and levodopa in a fixed ratio (1:10 or 1:4), is generally used. Treatment is started with a small dose—eg, one tablet of Sinemet 25/100 (containing 25 mg of carbidopa and 100 mg of levodopa) three times daily—and gradually increased depending on the response. Sinemet CR is a controlled-release formulation (containing 25 or 50 mg of carbidopa and 100 or 200 mg of levodopa). It is mainly useful when taken at bedtime to lessen motor disability upon awakening. A formulation of carbidopa/levodopa (Rytary) containing both immediate- and delayed-release beads provides a smoother response in patients with fluctuations. The commercially available combination of levodopa with both carbidopa and entacapone (Stalevo) may also be helpful in this context and is discussed in the following section on COMT inhibitors. Response fluctuations are also reduced by keeping the daily intake of protein at the recommended minimum and taking the main protein meal as the last meal of the day. A continuous infusion of a carbidopa-levodopa enteral suspension through a percutaneous gastrojejunostomy tube by a portable infusion pump reduces “off” time in patients with advanced Parkinson disease. Levodopa can also be taken by inhalation (Inbrija) as a rescue medication for patients developing severe akinesia (off periods). Benefit occurs about 10 minutes after inhalation. Side effects include cough, upper respiratory tract infection, nausea, and discolored sputum.

The dyskinesias and behavioral side effects of levodopa are dose-related, but reduction in dose may eliminate any therapeutic benefit. Levodopa-induced dyskinesias may also respond to amantadine.

Levodopa therapy is contraindicated in patients with psychotic illness or narrow-angle glaucoma. It should not be given to patients taking monoamine oxidase A inhibitors or within 2 weeks of their withdrawal, because hypertensive crises may result. Sudden discontinuation of levodopa can precipitate neuroleptic malignant syndrome and should be avoided.

3. Dopamine agonists—Dopamine agonists, such as pramipexole and ropinirole, act directly on dopamine receptors, and their use in parkinsonism is associated with a lower incidence of the response fluctuations and

dyskinesias that occur with long-term levodopa therapy. They are effective in both early and advanced stages of Parkinson disease. They are often given either before the introduction of levodopa or with a low dose of Sinemet 25/100 (carbidopa 25 mg and levodopa 100 mg, one tablet three times daily) when dopaminergic therapy is first introduced; the dose of Sinemet is kept constant, while the dose of the agonist is gradually increased.

Pramipexole is started at a dosage of 0.125 mg three times daily orally, and the dose is built up gradually to between 0.5 and 1.5 mg three times daily. Ropinirole is begun at 0.25 mg three times daily orally and gradually increased; most patients require between 2 and 8 mg three times daily for benefit. Extended-release, once-daily formulations of pramipexole and ropinirole have similar efficacy and tolerability as the immediate release versions. Rotigotine is a dopamine agonist absorbed transdermally from a skin patch; it is started at 2 mg once daily and increased weekly by 2 mg daily until achieving an optimal response, up to a maximum of 8 mg daily. Adverse effects of these various agonists include fatigue, somnolence, nausea, peripheral edema, dyskinesias, confusion, and postural hypotension. Less commonly, an irresistible urge to sleep may occur, sometimes in inappropriate and hazardous circumstances. Impulse control disorders involving gambling, shopping, or sexual activity also occur. Local skin reactions may occur with the rotigotine patch. The **dopamine agonist withdrawal syndrome** develops occasionally in patients in whom a dopamine agonist is tapered. It consists of a combination of distressing physical and psychological symptoms that are refractory to levodopa and other dopaminergic medications and may persist for months or longer. There is no effective treatment. The dopamine agonist should be reintroduced and tapered more gradually if possible.

4. Selective monoamine oxidase inhibitors—Rasagiline, a selective monoamine oxidase B inhibitor, has a clear symptomatic benefit in some patients at a daily oral dose of 1 mg, taken in the morning; it may also be used for adjunctive therapy in patients with response fluctuations to levodopa. Selegiline (5 mg orally with breakfast and lunch) and safinamide (50 mg orally daily, increased to 100 mg daily after 14 days) are also approved as adjunctive treatments. By inhibiting the metabolic breakdown of dopamine, these medications may improve fluctuations or declining response to levodopa.

Studies have suggested (but failed to show conclusively) that rasagiline may slow the progression of Parkinson disease, and it appears to delay the need for other symptomatic therapies. For these reasons, rasagiline is often started early, particularly for patients who are young or have mild disease. However, the FDA has rejected an expansion of rasagiline’s indication to include disease modification.

5. COMT inhibitors—Catecholamine-O-methyltransferase (COMT) inhibitors reduce the metabolism of levodopa to 3-O-methyldopa and thereby alter the plasma pharmacokinetics of levodopa, leading to more sustained plasma levels and more constant dopaminergic stimulation of the brain. Treatment with entacapone or tolcapone results in reduced

response fluctuations, with a greater period of responsiveness to administered levodopa. Tolcapone is given in a dosage of 100 mg or 200 mg three times daily orally, and entacapone is given as 200 mg with each dose of Sinemet. Opicapone, a long-acting, peripherally selective COMT inhibitor, is taken once daily (50 mg) at bedtime at least 1 hour before and after eating. The dose of Sinemet taken concurrently may have to be reduced by up to one-third to avoid side effects. Diarrhea is sometimes troublesome. Because rare cases of fulminant hepatic failure have followed its use, tolcapone should be avoided in patients with preexisting liver disease. Serial liver biochemical tests should be performed at 2-week intervals for the first year and at longer intervals thereafter in patients receiving the medication—as recommended by the manufacturer. Serious hepatotoxicity has not been reported with entacapone or opicapone.

Stalevo is the commercial preparation of levodopa combined with both carbidopa and entacapone. It is best used in patients already stabilized on equivalent doses of carbidopa/levodopa and entacapone. It is priced at or below the price of the individual ingredients (ie, carbidopa/levodopa and entacapone) and has the added convenience of requiring fewer tablets to be taken daily. It is available in three strengths: Stalevo 50 (12.5 mg of carbidopa, 50 mg of levodopa, and 200 mg of entacapone), Stalevo 100 (25 mg of carbidopa, 100 mg of levodopa, and 200 mg of entacapone), and Stalevo 150 (37.5 mg of carbidopa, 150 mg of levodopa, and 200 mg of entacapone).

6. Istradefylline—This adenosine A_{2A} receptor antagonist (20–40 mg orally once daily) is given to patients taking levodopa or a dopamine agonist to reduce off time; total off time is typically reduced by less than 1 hour per day.

7. Anticholinergic medications—Anticholinergics are more helpful in alleviating tremor and rigidity than bradykinesia. Trihexyphenidyl and benztrapine are commonly used formulations. Treatment is started with a small dose and gradually increased until benefit occurs or side effects limit further increments. If treatment is ineffective, the medication is gradually withdrawn and another preparation then tried. However, these medications are often poorly tolerated, especially in older adults.

Side effects limit the routine use of these medications, and include dryness of the mouth, nausea, constipation, palpitations, cardiac arrhythmias, urinary retention, confusion, agitation, restlessness, drowsiness, mydriasis, increased intraocular pressure, and defective accommodation. Anticholinergic medications are contraindicated in patients with prostatic hyperplasia, narrow-angle glaucoma, or obstructive gastrointestinal disease and are often tolerated poorly by the elderly. They are best avoided whenever cognitive impairment or a predisposition to delirium exists.

8. Antipsychotics—Confusion and psychotic symptoms may occur as a side effect of dopaminergic therapy or as a part of the underlying illness. Pimavanserin (34 mg once daily), a serotonin(2A) agonist, is approved by the FDA specifically for treating the psychosis of Parkinson disease. This may also respond to the atypical antipsychotic agents

clozapine and quetiapine, which have few extrapyramidal side effects and do not block the effects of dopaminergic medication. Clozapine may rarely cause marrow suppression, and weekly blood counts are therefore necessary for patients taking it. The patient is started on 6.25 mg at bedtime and the dosage increased to 25–100 mg/day as needed. In low doses, it may also improve iatrogenic dyskinesias. *Typical antipsychotic agents and the second-generation antipsychotic agents risperidone and olanzapine may cause worsening of motor symptoms and should be avoided.*

B. General Measures

Physical therapy or speech therapy helps many patients. Cognitive impairment and psychiatric symptoms may be helped by a cholinesterase inhibitor, such as rivastigmine (3–12 mg orally daily or 4.6 or 9.5 mg/24 hours transdermally daily). The quality of life can often be improved by the provision of simple aids to daily living, eg, rails or bannisters placed strategically about the home, special table cutlery with large handles, nonslip rubber table mats, and devices to amplify the voice.

C. Stimulation and Ablative Treatments

High-frequency stimulation of the subthalamic nuclei or globus pallidus internus may benefit many of the motor features of the disease but does not affect its natural history. Electrical stimulation of the brain has the advantage over ablative thalamotomy and pallidotomy procedures of being reversible and of causing minimal or no damage to the brain, and is therefore the preferred surgical approach to treatment. It is reserved for patients without cognitive impairment or psychiatric disorder who have a good response to levodopa, but in whom dyskinesias or response fluctuations are problematic. It frequently takes 3–6 months after surgery to adjust stimulator programming and to achieve optimal results. Side effects include depression, apathy, impulsivity, executive dysfunction, and decreased verbal fluency in a subset of patients. Focused ultrasound thalamotomy or stereotactic radiosurgery may help patients with medically refractory tremor-predominant parkinsonism who are reluctant to undergo surgery.

D. Gene Therapy

Injections of adeno-associated viruses encoding various human genes have been made into the subthalamic nucleus or putamen in various clinical trials. These approaches may be useful in the future but remain experimental.

► When to Refer

All patients should be referred.

► When to Admit

Patients requiring surgical treatment should be admitted.

Rughani A et al. Congress of Neurological Surgeons systematic review and evidence-based guideline on subthalamic nucleus and globus pallidus internus deep brain stimulation for the treatment of patients with Parkinson's disease: executive summary. *Neurosurgery*. 2018;82:753. [PMID: 29538685]

3. Huntington Disease



ESSENTIALS OF DIAGNOSIS

- ▶ Gradual onset and progression of chorea and dementia or behavioral change.
- ▶ Family history of the disorder.
- ▶ Responsible gene identified on chromosome 4.

► General Considerations

Huntington disease is characterized by *chorea and dementia*. It is inherited in an autosomal dominant manner and occurs throughout the world, in all ethnic groups, with a prevalence rate of about 5 per 100,000. There is an expanded and unstable CAG trinucleotide repeat in the huntingtin gene at 4p16.3; longer repeat lengths correspond to an earlier age of onset and faster disease progression.

► Clinical Findings

A. Symptoms and Signs

Clinical onset is usually between 30 and 50 years of age. The disease is progressive and usually leads to a fatal outcome within 15–20 years. The initial symptoms may consist of either abnormal movements or intellectual changes, but ultimately both occur. The earliest mental changes are often behavioral, with irritability, moodiness, antisocial behavior, or a psychiatric disturbance, but a more obvious dementia subsequently develops. The dyskinesia may initially be no more than an apparent fidgetiness or restlessness, but eventually choreiform movements and some dystonic posturing occur. A parkinsonian syndrome with progressive rigidity and akinesia (rather than chorea) sometimes occurs in association with dementia, especially in cases with childhood onset. The diagnosis is established with a widely available genetic test, although such testing should be pursued under the guidance of a licensed genetic counselor.

B. Imaging

CT scanning or MRI usually demonstrates cerebral atrophy and atrophy of the caudate nucleus in established cases. Positron emission tomography (PET) has shown reduced striatal metabolic rate.

► Differential Diagnosis

Chorea developing with no family history of choreoathetosis should not be attributed to Huntington disease, at least not until other causes of chorea have been excluded clinically

and by appropriate laboratory studies. Nongenetic causes of chorea include stroke, systemic lupus erythematosus and antiphospholipid antibody syndrome, paraneoplastic syndromes, infection with HIV, and various medications. In younger patients, self-limiting Sydenham chorea develops after group A streptococcal infections on rare occasions. If a patient presents solely with progressive intellectual failure, it may not be possible to distinguish Huntington disease from other causes of dementia unless there is a characteristic family history or a dyskinesia develops.

Huntington disease-like (HDL) disorders resemble Huntington disease but are caused by other genetic mutations. A clinically similar autosomal dominant disorder (**dentatorubral-pallidoluysian atrophy**), manifested by chorea, dementia, ataxia, and myoclonic epilepsy, is uncommon except in persons of Japanese ancestry. Treatment is as for Huntington disease.

► Treatment

There is no cure for Huntington disease; progression cannot be halted; and treatment is purely symptomatic, although studies of antisense oligonucleotides inhibiting production of mutant huntingtin protein are ongoing. The reported biochemical changes suggest a relative underactivity of neurons containing GABA and acetylcholine or a relative overactivity of dopaminergic neurons. Tetrabenazine, a medication that interferes with the vesicular storage of biogenic amines, is widely used to treat the dyskinesias. The starting dose is 12.5 mg twice or three times daily orally, increasing by 12.5 mg every 5 days depending on response and tolerance; the usual maintenance dose is 25 mg three times daily. Side effects include depression, postural hypotension, drowsiness, and parkinsonian features; tetrabenazine should not be given within 14 days of taking monoamine oxidase inhibitors and is not indicated for the treatment of levodopa-induced dyskinesias. Reserpine is similar in depleting central monoamines but has more peripheral effects and a worse side-effect profile, making its use problematic in Huntington disease; if utilized, the dose is built up gradually to between 2 mg and 5 mg orally daily, depending on the response. Deutetrabenazine is also effective in reducing chorea in Huntington disease and may have fewer side effects than tetrabenazine but direct comparisons are lacking. The starting dose is 6 mg once daily orally, increased to 6 mg twice daily after 1 week and by 6-mg increments weekly thereafter, to a maximum of 24 mg twice daily. Treatment with medications blocking dopamine receptors, such as phenothiazines or haloperidol, may control the dyskinesia and any behavioral disturbances. Haloperidol treatment is usually begun with a dose of 1 mg once or twice daily orally, which is then increased every 3 or 4 days depending on the response; alternatively, atypical antipsychotic agents such as quetiapine (increasing from 25 mg daily orally up to 100 mg twice daily orally as tolerated) may be tried. Amantadine in a dose of 200 mg to 400 mg daily orally is sometimes helpful for chorea. Deep brain stimulation has been used successfully to treat chorea in a small number of patients. Behavioral disturbances may respond to clozapine. Attempts to compensate for the relative GABA deficiency by enhancing central GABA activity

or to compensate for the relative cholinergic underactivity by giving choline chloride have not been therapeutically helpful.

Offspring should be offered genetic counseling. Genetic testing permits presymptomatic detection and definitive diagnosis of the disease.

► When to Refer

All patients should be referred.

Tabrizi SJ et al; Phase 1–2a IONIS-HTTRx Study Site Teams. Targeting huntingtin expression in patients with Huntington's disease. *N Engl J Med.* 2019;380:2307. [PMID: 31059641]

4. Idiopathic Torsion Dystonia



- ▶ Dystonic movements and postures.
- ▶ Normal birth and developmental history. No other neurologic signs.
- ▶ Investigations (including CT scan or MRI) reveal no cause of dystonia.

► General Considerations

Idiopathic torsion dystonia may occur sporadically or on a hereditary basis, with autosomal dominant, autosomal recessive, and X-linked recessive modes of transmission. Symptoms may begin in childhood or later and persist throughout life.

► Clinical Findings

The disorder is characterized by the onset of abnormal movements and postures in a patient with a normal birth and developmental history, no relevant past medical illness, and no other neurologic signs. Investigations (including CT scan) reveal no cause for the abnormal movements. Dystonic movements of the head and neck may take the form of torticollis, blepharospasm, facial grimacing, or forced opening or closing of the mouth. The limbs may also adopt abnormal but characteristic postures. The age at onset influences both the clinical findings and the prognosis. With onset in childhood, there is usually a family history of the disorder, symptoms commonly commence in the legs, and progression is likely until there is severe disability from generalized dystonia. In contrast, when onset is later, a positive family history is unlikely, initial symptoms are often in the arms or axial structures, and severe disability does not usually occur, although generalized dystonia may ultimately develop in some patients. If all cases are considered together, about one-third of patients eventually become so severely disabled that they are confined to chair or bed, while another one-third are affected only mildly.

► Differential Diagnosis

Perinatal anoxia, birth trauma, and kernicterus are common causes of dystonia, but abnormal movements usually then develop before the age of 5, the early development of the patient is usually abnormal, and a history of seizures is not unusual. Moreover, examination may reveal signs of mental retardation or pyramidal deficit in addition to the movement disorder. Dystonic posturing may also occur in Wilson disease, Huntington disease, or parkinsonism; as a sequela of encephalitis lethargica or previous neuroleptic medication therapy; and in certain other disorders. In these cases, diagnosis is based on the history and accompanying clinical manifestations.

► Treatment

Idiopathic torsion dystonia usually responds poorly to medications. A distinct variety of dominantly inherited dystonia is remarkably responsive to levodopa; therefore, a levodopa trial is warranted in all patients. Failing this, diazepam, baclofen, carbamazepine, amantadine, or anticholinergic medication such as trihexyphenidyl or benzotropine (in high dosage) is occasionally helpful; if not, a trial of treatment with tetrabenazine, phenothiazines, or haloperidol may be worthwhile. In each case, the dose has to be individualized, depending on response and tolerance. However, the doses of these latter medications that are required for benefit lead usually to mild parkinsonism. Pallidal deep brain stimulation is helpful for disabling generalized dystonia and has a lower morbidity than stereotactic thalamotomy, which is sometimes helpful in patients with predominantly unilateral limb dystonia. Potential adverse events of deep brain stimulation include cerebral infection or hemorrhage, broken leads, affective changes, and dysarthria.

► When to Refer

All patients should be referred.

► When to Admit

Patients requiring surgical treatment should be admitted.

Rodrigues FB et al. Deep brain stimulation for dystonia. *Cochrane Database Syst Rev.* 2019;1:CD012405. [PMID: 30629283]

5. Focal Torsion Dystonia

A number of the dystonic manifestations that occur in idiopathic torsion dystonia may also occur as isolated phenomena. They are best regarded as focal dystonias that either occur as forms frustes of idiopathic torsion dystonia in patients with a positive family history or represent a focal manifestation of the adult-onset form of that disorder when there is no family history. Medical treatment is generally unsatisfactory. A trial of the medications used in idiopathic torsion dystonia is worthwhile, however, since a few patients do show some response. In addition, with restricted dystonias such as blepharospasm or torticollis, local injection of botulinum A toxin into the overactive

muscles may produce worthwhile benefit for several weeks or months and can be repeated as needed.

Both **blepharospasm** and **oromandibular dystonia** may occur as an isolated focal dystonia. The former is characterized by spontaneous involuntary forced closure of the eyelids for a variable interval. Oromandibular dystonia is manifested by involuntary contraction of the muscles about the mouth causing, for example, involuntary opening or closing of the mouth, roving or protruding tongue movements, and retraction of the platysma. **Cervical dystonia** (spasmodic torticollis), usually with onset between 25 and 50 years of age, is characterized by a tendency for the neck to twist to one side. This initially occurs episodically, but eventually the neck is held to the side. Some patients have a sensory trick ("geste antagoniste") that lessens the dystonic posture, eg, touching the side of the face. Spontaneous resolution may occur in the first year or so. The disorder is otherwise usually lifelong. Local injection of botulinum A toxin provides benefit in most cases. Deep brain stimulation of the globus pallidus interna is an option if medical treatment and botulinum toxin injection are unsuccessful.

Writer's cramp is characterized by dystonic posturing of the hand and forearm when the hand is used for writing and sometimes when it is used for other tasks, eg, playing the piano or using a screwdriver or eating utensils. Medication treatment is usually unrewarding, and patients are often best advised to learn to use the other hand for activities requiring manual dexterity. Injections of botulinum A toxin are helpful in some instances.

Rodrigues FB et al. Botulinum toxin type A therapy for cervical dystonia. Cochrane Database Syst Rev. 2020;11:CD003633. [PMID: 33180963]

6. Myoclonus

Occasional myoclonic jerks may occur in anyone, especially when drifting into sleep. **General or multifocal myoclonus** is common in patients with idiopathic epilepsy and is especially prominent in certain hereditary disorders characterized by seizures and progressive intellectual decline, such as the lipid storage diseases. It is also a feature of subacute sclerosing panencephalitis and Creutzfeldt-Jakob disease. Generalized myoclonic jerking may accompany uremic and other metabolic encephalopathies, result from therapy with levodopa or tricyclic antidepressants, occur in alcohol or drug withdrawal states, or follow anoxic brain damage. It also occurs on a hereditary or sporadic basis as an isolated phenomenon in otherwise healthy subjects.

Segmental myoclonus is a rare manifestation of a focal spinal cord lesion. It may also be the clinical expression of **epilepsia partialis continua**, a disorder in which a repetitive focal epileptic discharge arises in the contralateral sensorimotor cortex, sometimes from an underlying structural lesion. An electroencephalogram is often helpful in clarifying the epileptic nature of the disorder, and CT or MRI scan may reveal the causal lesion.

Myoclonus may respond to certain anticonvulsant medications, especially valproic acid or levetiracetam, or to

one of the benzodiazepines, particularly clonazepam (see Table 24-2). It may also respond to piracetam (up to 16.8 g daily; not available in the United States). Myoclonus following anoxic brain damage is often responsive to oxitriptan (5-hydroxytryptophan), the precursor of serotonin, and sometimes to clonazepam. Oxitriptan is given in gradually increasing doses up to 1–1.5 mg daily. In patients with segmental myoclonus, a localized lesion should be searched for and treated appropriately.

7. Wilson Disease

In this metabolic disorder, abnormal movement and posture may occur with or without coexisting signs of liver involvement. Psychiatric and neuropsychological manifestations are common. Wilson disease is discussed in Chapter 16.

8. Drug-Induced Abnormal Movements

Phenothiazines, butyrophenones, and metoclopramide may produce a wide variety of abnormal movements, including parkinsonism, akathisia (ie, motor restlessness), acute dystonia, chorea, and tardive dyskinesias or dystonia; several of these are also produced by aripiprazole. These complications are discussed in Chapter 25. Chorea may also develop in patients receiving levodopa, bromocriptine, anticholinergic medications, phenytoin, carbamazepine, lithium, amphetamines, or oral contraceptives, and it resolves with withdrawal of the offending substance. Similarly, dystonia may be produced by levodopa, bromocriptine, lithium, or carbamazepine; and parkinsonism by reserpine and tetrabenazine. Postural tremor may occur with a variety of medications, including epinephrine, isoproterenol, amiodarone, theophylline, caffeine, lithium, thyroid hormone, tricyclic antidepressants, and valproic acid.

9. Restless Legs Syndrome

This common disorder, affecting 1–5% of people, may occur as a primary (idiopathic) disorder or in relation to Parkinson disease, pregnancy, iron deficiency anemia, or peripheral neuropathy (especially uremic or diabetic). It may have a hereditary basis, and several genetic loci have been associated with the disorder. Restlessness and curious sensory disturbances lead to an irresistible urge to move the limbs, especially during periods of relaxation; movement of the limbs provides relief. The urge occurs exclusively in the evening and at night or is worse at night than during the day. Most patients also have **periodic limb movements of sleep** and one-third have periodic limb movements during relaxed wakefulness; both consist of brief involuntary flexion at the ankle, knee, and hip. Disturbed nocturnal sleep and excessive daytime somnolence may result. Ferritin levels should always be measured; treatment with oral iron sulfate in patients with ferritin levels less than or equal to 75 mcg/L (13.4 mcmol/L) should be attempted prior to initiation of other pharmacotherapies. Therapy is with nonergot dopamine agonists, such as pramipexole (0.125–0.5 mg orally once daily),

ropinirole (0.25–4 mg orally once daily 2 to 3 hours before bedtime), or rotigotine (1–3 mg/24 h transdermal patch once daily), or with gabapentin enacarbil (300–1200 mg orally each evening). Gabapentin (starting with 300 mg orally daily, increasing to approximately 1800 mg daily depending on response and tolerance) and pregabalin (150–300 mg orally divided twice to three times daily) are related medications that improve symptoms. Levodopa is helpful but may lead to an augmentation of symptoms, so its use is generally reserved for those who do not respond to other measures. Extended-release oxycodone-naloxone (2.5–5 mg to 5–10 mg orally twice daily) is useful in patients with severe symptoms or those who are refractory to first-line therapies.

Winkelmann J et al. Treatment of restless legs syndrome: evidence-based review and implications for clinical practice. *Mov Disord.* 2018;33:1077. [PMID: 29756335]

10. Gilles De La Tourette Syndrome

ESSENTIALS OF DIAGNOSIS

- ▶ Multiple motor and phonic tics.
- ▶ Symptoms begin before age 18 years.
- ▶ Tics occur frequently for at least 1 year.
- ▶ Tics vary in number, frequency, and nature over time.

Clinical Findings

Simple tics occur transiently in up to 25% of children, remit within weeks to months, and do not require treatment. Tourette syndrome is a more complex disorder. **Motor tics** are the initial manifestation in 80% of cases and most commonly involve the face, whereas in the remaining 20%, the initial symptoms are **phonic tics**; ultimately a combination of different motor and phonic tics develop in all patients. Tics are preceded by an urge that is relieved upon performance of the movement or vocalization; they can be temporarily suppressed but eventually the urge becomes overwhelming. These are noted first in childhood, generally between the ages of 2 and 15. Motor tics occur especially about the face, head, and shoulders (eg, sniffing, blinking, frowning, shoulder shrugging, head thrusting, etc). Phonic tics commonly consist of grunts, barks, hisses, throat-clearing, coughs, etc, but sometimes also of verbal utterances including coprolalia (obscene speech). There may also be echolalia (repetition of the speech of others), echopraxia (imitation of others' movements), and palilalia (repetition of words or phrases). Some tics may be self-mutilating in nature, such as nail-biting, hair-pulling, or biting of the lips or tongue. The disorder is chronic, but the course may be punctuated by relapses and remissions. Obsessive-compulsive disorder (OCD) and attention deficit hyperactivity disorder (ADHD) are commonly associated and may be more dis-

abling than the tics themselves. A family history is sometimes obtained.

Examination usually reveals no abnormalities other than the tics. In addition to OCD, psychiatric disturbances may occur because of the associated cosmetic and social embarrassment. The diagnosis of the disorder is often delayed for years, the tics being interpreted as psychiatric illness or some other form of abnormal movement. Patients are thus often subjected to unnecessary treatment before the disorder is recognized. The tic-like character of the abnormal movements and the absence of other neurologic signs should differentiate this disorder from other movement disorders presenting in childhood. Wilson disease, however, can simulate the condition and should be excluded.

Treatment

Treatment is symptomatic and may need to be continued indefinitely. Habit reversal training or other forms of behavioral therapy can be effective alone or in combination with pharmacotherapy. Alpha-adrenergic agonists, such as clonidine (start 0.05 mg orally at bedtime, titrating to 0.3–0.4 mg orally daily, divided three to four times per day) or guanfacine (start 0.5 mg orally at bedtime, titrating to a maximum of 3–4 mg orally daily, divided twice daily), are first-line therapies because of a favorable side-effect profile compared with typical antipsychotics, which are the only FDA-approved therapies for the disorder. They also have the advantage of improving the symptoms of concomitant ADHD. Many specialists favor the use of tetrabenazine. The atypical antipsychotic risperidone (1–6 mg daily orally) is more effective than placebo in controlling tics and more effective than pimozide in improving symptoms of comorbid OCD and may be tried before the typical antipsychotic agents. When a typical antipsychotic is required in cases of severe tics, haloperidol is generally regarded as the medication of choice. It is started in a low dose (0.25 mg daily orally) that is gradually increased (by 0.25 mg every 4 or 5 days) until there is maximum benefit with a minimum of side effects or until side effects limit further increments. A total daily oral dose of between 2 mg and 8 mg is usually optimal, but higher doses are sometimes necessary. Fluphenazine (1–15 mg orally daily) and pimozide (1–10 mg orally daily) are alternatives. Typical antipsychotics can cause significant weight gain and carry a risk of tardive dyskinesias and other long-term, potentially irreversible motor side effects. Small randomized trials or observational studies have reported benefit from topiramate, nicotine, tetrahydrocannabinol, baclofen, and clonazepam. A number of other medications, including deutetetrabenazine, valbenazine, and ecopipam, are being studied for the treatment of tics.

Injection of botulinum toxin type A at the site of the most distressing tics is sometimes worthwhile and has fewer side effects than systemic antipsychotic therapy. Bilateral high-frequency deep brain stimulation at various sites has been helpful in some, otherwise intractable, cases.

When to Refer

All patients should be referred.

► When to Admit

Patients undergoing surgical (deep brain stimulation) treatment should be admitted.

Martinez-Ramirez D et al. Efficacy and safety of deep brain stimulation in Tourette syndrome: the International Tourette Syndrome Deep Brain Stimulation Public Database and Registry. *JAMA Neurol.* 2018;75:353. [PMID: 29340590]

Pringsheim T et al. Practice guideline recommendations summary: treatment of tics in people with Tourette syndrome and chronic tic disorders. *Neurology.* 2019;92:896. [PMID: 31061208]

DEMENTIA

ESSENTIALS OF DIAGNOSIS

- ▶ Progressive intellectual decline.
- ▶ Not due to delirium or psychiatric disease.
- ▶ Age is the main risk factor, followed by family history and vascular disease risk factors.

Table 24–6. Common causes of age-related dementia (listed by prevalence).

Disorder	Pathology	Clinical Features
Alzheimer disease	Plaques containing beta-amyloid peptide, and neurofibrillary tangles containing tau protein, occur throughout the neocortex.	<ul style="list-style-type: none"> • Most common age-related neurodegenerative disease; incidence doubles every 5 years after age 60. • Short-term memory impairment is early and prominent in most cases. • Variable deficits of executive function, visuospatial function, and language.
Vascular dementia	Multifocal ischemic change.	<ul style="list-style-type: none"> • Stepwise or progressive accumulation of cognitive deficits in association with repeated strokes. • Symptoms depend on localization of strokes.
Dementia with Lewy bodies	Histologically indistinguishable from Parkinson disease: alpha-synuclein-containing Lewy bodies occur in the brainstem, midbrain, olfactory bulb, and neocortex. Alzheimer pathology may coexist.	<ul style="list-style-type: none"> • Cognitive dysfunction, with prominent visuospatial and executive deficits. • Psychiatric disturbance, with anxiety, visual hallucinations, and fluctuating delirium. • Parkinsonian motor deficits with or after other features. • Cholinesterase inhibitors lessen delirium; poor tolerance of neuroleptics and dopaminergics.
Frontotemporal dementia (FTD)	Neuropathology is variable and defined by the protein found in intraneuronal aggregates. Tau protein, TAR DNA-binding protein 43 (TDP-43), or fused-in-sarcoma (FUS) protein account for most cases.	<ul style="list-style-type: none"> • Peak incidence in the sixth decade; approximately equal to Alzheimer disease as a cause of dementia in patients under 60 years old. • Familial cases result from mutations in genes for tau, progranulin, or others. <p>Behavioral variant FTD</p> <ul style="list-style-type: none"> • Deficits in empathy, social comportment, insight, abstract thought, and executive function. • Behavior is disinhibited, impulsive, and ritualistic, with prominent apathy and increased interest in sex or sweet/fatty foods. • Relative preservation of memory. • Focal right frontal atrophy. • Association with amyotrophic lateral sclerosis. <p>Semantic variant primary progressive aphasia</p> <ul style="list-style-type: none"> • Deficits in word-finding, single-word comprehension, object and category knowledge, and face recognition. • Behaviors may be similar to behavioral variant FTD. • Focal, asymmetric temporal pole atrophy. <p>Nonfluent/agrammatic variant primary progressive aphasia</p> <ul style="list-style-type: none"> • Speech is effortful with dysarthria, phonemic errors, sound distortions, and poor grammar. • Focal extrapyramidal signs and apraxia of the right arm and leg are common; overlaps with corticobasal degeneration. • Focal left frontal atrophy.

Physical activity seems to be protective; education, ongoing intellectual stimulation, and social engagement may also be protective, perhaps by promoting *cognitive reserve*, an improved capacity to compensate for insidious neurodegeneration.

Dementia is distinct from delirium and psychiatric disease. **Delirium** is an acute confusional state that often occurs in response to an identifiable trigger, such as drug or alcohol intoxication or withdrawal (eg, Wernicke encephalopathy, described below), medication side effects (especially medications with anticholinergic properties, antihistamines, benzodiazepines, sleeping aids, opioids, neuroleptics, corticosteroids, and other sedative or psychotropic agents), infection (consider occult urinary tract infection or pneumonia in elderly patients), metabolic disturbance (including an electrolyte abnormality; hypoglycemia or hyperglycemia; or a nutritional, endocrine, renal, or hepatic disorder), sleep deprivation, or other neurologic disease (seizure, including a postictal state, or stroke). Delirium typically involves *fluctuating* levels of arousal, including drowsiness or agitation, and it improves after removal or treatment of the precipitating factor. Patients with dementia are especially susceptible to episodes of delirium, but recognition of dementia is not possible until delirium lifts. For this reason, dementia is typically diagnosed in outpatients who are otherwise medically stable, rather than in acutely ill patients in the hospital.

Psychiatric disease sometimes leads to complaints of impaired cognition (**pseudodementia**). Impaired attention is usually to blame, and in some patients with depression or anxiety, poor focus and concentration may even be a primary complaint. The symptoms should improve with appropriate psychiatric treatment. Mood disorders are commonly seen in patients with neurodegenerative disease and in some cases are an early symptom. There is some evidence that a persistent, untreated mood disorder may predispose to the development of an age-related dementia, and psychiatric symptoms can clearly exacerbate cognitive impairment in patients who already have dementia; therefore, suspicion of dementia should not distract from appropriate screening for and treatment of depression or anxiety.

► Clinical Findings

A. Symptoms and Signs

Symptoms and signs of the common causes of dementia are detailed in Table 24–6. Clinicians should be aware that a patient's insight into a cognitive change may be vague or absent, and collateral history is essential to a proper evaluation. As patients age, primary care clinicians should inquire periodically about the presence of any cognitive symptoms.

Symptoms depend on the area of the brain affected. **Short-term memory loss**, involving the repeating of questions or stories and a diminished ability to recall the details of recent conversations or events, frequently results from pathologic changes in the hippocampus. **Word-finding difficulty** often involves difficulty recalling the names of people, places, or objects, with low-frequency words affected first, eventually resulting in speech laden with pronouns and circumlocutions. This problem is thought to arise from

pathology at the temporoparietal junction of the left hemisphere. Problems with articulation, fluency, comprehension, or word meaning are anatomically distinct and less common. **Visuospatial dysfunction** may result in poor navigation and getting lost in familiar places, impaired recognition of previously familiar faces and buildings, or trouble discerning an object against a background. The right parietal lobe is one of the brain areas implicated in such symptoms. **Executive dysfunction** may manifest by easy distractibility, impulsivity, mental inflexibility, concrete thought, slowed processing speed, poor planning and organization, or impaired judgment. Localization may vary and could include the frontal lobes or subcortical areas like the basal ganglia or cerebral white matter. **Apathy** or indifference, separate from depression, is common and may have a similar anatomy as executive dysfunction. **Apraxia**, or the loss of learned motor behaviors, may result from dysfunction of the frontal or parietal lobes, especially the left parietal lobe.

The time of symptom onset must be established, but subtle, early symptoms are often apparent only in retrospect. Another event, such as an illness or hospitalization, may lead to new recognition of existing symptoms. Symptoms often accumulate over time, and *the nature of the earliest symptom is most helpful in forming the differential diagnosis*. The history should establish risk factors for dementia, including family history, other chronic illnesses, and vascular disease risk factors. Finally, it is important to document the patient's current capacity to perform **basic and instrumental activities of daily living** (see Chapter 4) and to note the extent of decline from the premorbid level of function. Indeed, it is this functional assessment that defines the presence and severity of dementia.

The physical examination is important to identify any occult medical illness. In addition, eye movement abnormalities, parkinsonism, or other motor abnormalities may help identify an underlying neurologic condition. The workup should prioritize the exclusion of conditions that are reversible or require separate therapy. Screening for depression is necessary, along with imaging and laboratory workup, as indicated below.

B. Neuropsychological Assessment

Brief quantification of cognitive impairment is indicated in a patient complaining of cognitive symptoms or if caregivers raise similar concerns. The **Folstein Mini Mental State Exam (MMSE)**, **Montreal Cognitive Assessment (MoCA)**, Mini-Cog, and other similar tests are brief, objective, and widely used but have important limitations: they are insensitive to mild cognitive impairment, they may be biased negatively by the presence of language or attention problems, and they do not correlate with functional capacity.

A neuropsychiatric evaluation by a trained neuropsychologist or psychometrician may be appropriate. The goal of such testing is to enhance localization by defining the cognitive domains that are impaired as well as to quantify the degree of impairment. There is no standard battery of tests, but a variety of metrics is commonly used to assess the symptom types highlighted above. Assessments are most accurate when a patient is well rested, comfortable, and otherwise medically stable.

C. Imaging

Brain imaging with MRI or CT without contrast is indicated in any patient with a new, progressive cognitive complaint. The goal is to exclude occult cerebrovascular disease, tumor, or other identifiable structural abnormality, rather than to provide positive evidence of a neurodegenerative disease. Global or focal brain atrophy may be worse than expected for age and could suggest a particular neurodegenerative process, but such findings are rarely specific.

PET with fluorodeoxyglucose (FDG) does not confirm or exclude any specific cause of dementia but may be useful as an element of the workup in specific clinical circumstances, such as discriminating between Alzheimer disease and frontotemporal dementia in a patient with some symptoms of each. PET imaging with a radiolabeled ligand for beta-amyloid, one of the pathologic proteins in Alzheimer disease, is highly sensitive to amyloid pathology and may provide positive evidence for Alzheimer disease in a patient with cognitive decline. However, after age 60 or 70, amyloid plaques can accumulate in the absence of cognitive impairment; thus, the specificity of a positive amyloid scan diminishes with age. Single-photon emission computed tomography offers similar information as FDG-PET but is less sensitive. PET imaging with radiolabeled ligands for tau, a pathogenic protein in Alzheimer disease, progressive supranuclear palsy, and some forms of frontotemporal dementia, also may help refine premortem diagnostic accuracy.

D. Laboratory Findings

Serum levels of vitamin B₁₂, free T₄, and thyroid-stimulating hormone should be measured for any patient with cognitive symptoms. A serum rapid plasma reagin (RPR) and testing for HIV should be considered. Other testing should be driven by clinical suspicion, and often includes a complete blood count, serum electrolytes, glucose, and lipid profile.

Although the presence of one or two ApoE epsilon-4 alleles indicates an increased risk of Alzheimer disease and ApoE genotyping is clinically available, it is of *limited clinical utility*. Finding an ApoE epsilon-4 allele in a young patient with dementia might raise the index of suspicion for Alzheimer disease, but obtaining a genotype in an elderly patient is unlikely to be helpful, and doing so in an asymptomatic patient as a marker of risk for Alzheimer disease is inappropriate until a preventive therapy becomes available. Spinal fluid protein measurements are also available and may support the diagnosis of Alzheimer disease in the appropriate clinical context; levels of beta-amyloid decrease and tau protein increase in Alzheimer disease, but this testing shares some of the same concerns as amyloid PET imaging.

► Differential Diagnosis

In elderly patients with gradually progressive cognitive symptoms and no other complaint or sign, a neurodegenerative disease is likely (Table 24–6). Decline beginning before age 60, rapid progression, fluctuating course, unintended weight loss, systemic complaints, or other

unexplained symptoms or signs raise suspicion for a process other than a neurodegenerative disease. In this case, the differential is broad and includes infection or inflammatory disease (consider a lumbar puncture to screen for cells or antibodies in the spinal fluid), neoplasm or a paraneoplastic condition, endocrine or metabolic disease, drugs or toxins, or other conditions. Normal pressure hydrocephalus is a difficult diagnosis to establish. Symptoms include gait apraxia (sometimes described as a “magnetic” gait, as if the feet are stuck to the floor), urinary incontinence, and dementia. CT scanning or MRI of the brain reveals ventricles that are enlarged in obvious disproportion to sulcal widening and overall brain atrophy.

► Treatment

A. Nonpharmacologic Approaches

Aerobic exercise (30 minutes several days per week) may reduce the rate of functional decline and decrease the demented patient's caregiving needs and may reduce the risk of dementia in normal individuals. Maintaining as active a role in the family and community as practically possible is likely to be of benefit, emphasizing activities at which the patient feels confident. Patients with neurodegenerative diseases have a limited capacity to regain lost skills; for instance, memory drills in a patient with Alzheimer disease are more likely to lead to frustration than benefit and studies show that computerized cognitive training does *not* improve cognition or function in demented patients. Vitamin E (1000 international units twice daily) appears to reduce the rate of functional decline in patients with Alzheimer disease, but does not affect cognition or prevent the development of Alzheimer disease in patients with mild cognitive impairment.

B. Cognitive Symptoms

Cholinesterase inhibitors are first-line therapy for Alzheimer disease and dementia with Lewy bodies (Table 24–6). They provide modest, symptomatic treatment for cognitive dysfunction and may prolong the capacity for independence but do *not* prevent disease progression. Commonly used medications include donepezil (start at 5 mg orally daily for 4 weeks, then increase to 10 mg daily; a 23 mg daily dose is approved for moderate to severe Alzheimer disease, although its very modest additional efficacy over the 10 mg dose is overshadowed by an increased risk of side effects); rivastigmine (start at 1.5 mg orally twice daily, then increasing every 2 weeks by 1.5 mg twice daily to a goal of 3–6 mg twice daily; or 4.6, 9.5, or 13.3 mg/24 h transdermally daily); and galantamine (start at 4 mg orally twice daily, then increasing every 4 weeks by 4 mg twice daily to a goal of 8–12 mg twice daily; a once-daily extended-release formulation is also available). Cholinesterase inhibitors are *not* given for frontotemporal dementia because they may worsen behavioral symptoms. Nausea and diarrhea are common side effects; syncope and cardiac dysrhythmia are uncommon but more serious. An ECG is often obtained before and after starting therapy, particularly in a patient with cardiac disease or a history of syncope.

Memantine (start at 5 mg orally daily, then increase by 5 mg per week up to a target of 10 mg twice daily) is approved for the treatment of moderate to severe Alzheimer disease. In frontotemporal dementia, memantine is ineffective and may worsen cognition. There is some evidence that memantine may improve cognition and behavior among patients with dementia with Lewy bodies.

Disease-modifying medications are not yet available for Alzheimer disease.

C. Mood and Behavioral Disturbances

Selective serotonin reuptake inhibitors are generally safe and well tolerated in elderly, cognitively impaired patients, and they may be efficacious for the treatment of depression, anxiety, or agitation. There is evidence to support the use of citalopram (10–30 mg orally daily) for agitation; side effects include QTc prolongation and worsened cognition at the highest dose. Paroxetine should be avoided because it has anticholinergic effects; avoid all tricyclic antidepressants for the same reason. Other antidepressant agents, such as bupropion or venlafaxine, may be tried.

Insomnia is common, and trazodone (25–50 mg orally at bedtime as needed) can be safe and effective. Over-the-counter antihistamine hypnotics must be avoided, along with benzodiazepines, because of their tendency to worsen cognition and precipitate delirium. Other prescription hypnotics such as zolpidem may result in similar adverse reactions.

For agitation, impulsivity, and other behaviors that interfere with safe caregiving, causes of delirium (detailed above) should first be considered. When no reversible trigger is identified, treatment should be approached in a staged manner. Behavioral interventions, such as reorientation and distraction from anxiety-provoking stimuli, are first-line. Ensure that the patient is kept active during the day with both physical exercise and mentally stimulating activities, and that there is adequate sleep at night. Reassess the level of caregiving, and consider increasing the time spent directly with an attendant. Next, ensure that appropriate pharmacologic treatment of cognition and mood is optimized. Finally, as a last resort, when other measures prove insufficient and the patient's behaviors raise safety concerns, consider pharmacologic therapy. Citalopram or low doses of an atypical antipsychotic medication such as quetiapine (start 25 mg orally daily as needed, increasing to two to three times daily as needed) can be tried; even though atypical agents cause extrapyramidal side effects less frequently than typical antipsychotics, they should be used with particular caution in a patient at risk for falls, especially if parkinsonian signs are already present. Regularly scheduled dosing of antipsychotics is not recommended, and if implemented should be reassessed on a frequent basis (eg, weekly), with attempts to taper off as tolerated. There is an FDA black box warning against the use of all antipsychotic medications in elderly demented patients because of an increased risk of death; the reason for the increased mortality is unclear. The combination of dextromethorphan and quinidine (up to 30/10 mg orally twice daily) has shown promise in early clinical trials.

► Special Circumstances

A. Rapidly Progressive Dementia

When dementia develops quickly, with obvious decline over a few weeks to a few months, the syndrome may be classified as a **rapidly progressive dementia**. The differential diagnosis for typical dementias is still relevant, but additional etiologies must be considered, including prion disease; infections; toxins; neoplasms; and autoimmune and inflammatory diseases, including corticosteroid-responsive (Hashimoto) encephalopathy and antibody-mediated paraneoplastic and nonparaneoplastic encephalitis (Table 24–5). Workup should begin with brain MRI with contrast and diffusion-weighted imaging, routine laboratory studies (serum vitamin B₁₂, free T₄, and thyroid-stimulating hormone levels), serum RPR, HIV antibody, Lyme serology, rheumatologic tests (erythrocyte sedimentation rate, C-reactive protein, and antinuclear antibody), anti-thyroglobulin and anti-thyroperoxidase antibody levels, paraneoplastic and nonparaneoplastic autoimmune antibodies (Table 24–5), and cerebrospinal fluid studies (cell count and differential; protein and glucose levels; protein electrophoresis for oligoclonal bands; IgG index [spinal-fluid-to-serum-gamma-globulin level] ratio; and VDRL). Depending on the clinical context, it may be necessary to exclude Wilson disease (24-hour urine copper level); heavy metal intoxication (urine heavy metal panel); and infectious encephalitis due to atypical bacteria, viruses, fungi, and mycobacteria.

Creutzfeldt-Jakob disease is a relatively common cause of rapidly progressive dementia (see Chapter 32). Family history is important since mutations in *PRNP*, the gene for the prion protein, account for around 15% of cases. Diffusion-weighted MRI is the most helpful diagnostic tool, classically revealing cortical ribboning (a gyral pattern of hyperintensity) as well as restricted diffusion in the caudate and anterior putamen. An electroencephalogram often shows periodic complexes. Real time quaking induced conversion (RT-QuIC), in which patient cerebrospinal fluid is mixed with recombinant prion protein and aggregation of prion protein is detected, is a sensitive and specific diagnostic test. Reflecting the high rate of neuronal death, cerebrospinal fluid levels of the intraneuronal proteins tau, 14-3-3, and neuron-specific enolase are often elevated, although this finding is neither sensitive nor specific.

B. Driving and Dementia

It is recommended that *any patient with mild dementia or worse should discontinue driving*. Most states have laws regulating driving among cognitively impaired individuals, and many require the clinician to report the patient's diagnosis to the public health department or department of motor vehicles. There is no evidence that driving classes help patients with neurodegenerative diseases.

► When to Refer

All patients with new, unexplained cognitive decline should be referred.

► When to Admit

Admission to the hospital should only occur when essential in patients with dementia due to increased risk of developing hospital-acquired delirium.

Arvanitakis Z et al. Diagnosis and management of dementia: review. *JAMA*. 2019;322:1589. [PMID: 31638686]

Law CK et al. Physical exercise attenuates cognitive decline and reduces behavioral problems in people with mild cognitive impairment and dementia: a systematic review. *J Physiother*. 2020;66:9. [PMID: 31843427]

WERNICKE ENCEPHALOPATHY & KORSAKOFF SYNDROME

Wernicke encephalopathy is characterized by confusion, ataxia, and nystagmus leading to ophthalmoplegia (lateral rectus muscle weakness, conjugate gaze palsies); peripheral neuropathy may also be present. It is *due to thiamine deficiency* and in the United States occurs most commonly in patients with alcoholism. It may also occur in patients with AIDS or hyperemesis gravidarum, and after bariatric surgery. In suspected cases, thiamine (100 mg) is given intravenously immediately and then intramuscularly on a daily basis until a satisfactory diet can be ensured after which the same dose is given orally. Some guidelines recommend initial doses of 200–500 mg intravenously three times daily for the first 5–7 days of treatment. Intravenous glucose given *before* thiamine may precipitate the syndrome or worsen the symptoms. The diagnosis is confirmed by the response in 1 or 2 days to treatment, which must not be delayed while awaiting laboratory confirmation of thiamine deficiency from a blood sample obtained prior to thiamine administration. **Korsakoff syndrome** occurs in more severe cases; it includes anterograde and retrograde amnesia and sometimes confabulation, and may not be recognized until after the initial delirium has lifted.

STUPOR & COMA



ESSENTIALS OF DIAGNOSIS

- ▶ Level of consciousness is depressed.
- ▶ Stuporous patients respond only to repeated vigorous stimuli.
- ▶ Comatose patients are unarousable and unresponsive.

► General Considerations

The patient who is **stuporous** is unresponsive except when subjected to repeated vigorous stimuli, while the **comatose** patient is unarousable and unable to respond to external events or inner needs, although reflex movements and posturing may be present.

Coma is a major complication of serious central nervous system disorders. It can result from seizures,

hypothermia, metabolic disturbances, or structural lesions causing bilateral cerebral hemispheric dysfunction or a disturbance of the brainstem reticular activating system. A mass lesion involving one cerebral hemisphere may cause coma by compression of the brainstem.

► Assessment & Emergency Measures

The diagnostic workup of the comatose patient must proceed concomitantly with management. Supportive therapy for respiration or blood pressure is initiated; in hypothermia, all vital signs may be absent and all such patients should be rewarmed before the prognosis is assessed.

The patient can be positioned on one side with the neck partly extended, dentures removed, and secretions cleared by suction; if necessary, the patency of the airways is maintained with an oropharyngeal airway. Blood is drawn for serum glucose, electrolyte, and calcium levels; arterial blood gases; liver biochemical and kidney function tests; and toxicologic studies as indicated. Thiamine (100 mg), followed by dextrose 50% (25 g), and naloxone (0.4–1.2 mg) are given intravenously without delay.

Further details are then obtained from attendants of the patient's medical history, the circumstances surrounding the onset of coma, and the time course of subsequent events. Abrupt onset of coma suggests subarachnoid hemorrhage, brainstem stroke, or intracerebral hemorrhage, whereas a slower onset and progression occur with other structural or mass lesions. Urgent noncontrast CT scanning of the head is appropriate if it can be obtained directly from the emergency department, in order to identify intracranial hemorrhage, brain herniation, or other structural lesion that may require immediate neurosurgical intervention. A metabolic cause is likely with a preceding intoxicated state or agitated delirium. On examination, attention is paid to the behavioral response to painful stimuli, the pupils and their response to light, the response to touching the cornea with a wisp of sterile gauze, position of the eyes and their movement in response to passive movement of the head and ice-water caloric stimulation, and the respiratory pattern.

A. Response to Painful Stimuli

Purposeful limb withdrawal from painful stimuli implies that sensory pathways from and motor pathways to the stimulated limb are functionally intact. Unilateral absence of responses despite application of stimuli to both sides of the body in turn implies a corticospinal lesion; bilateral absence of responsiveness suggests brainstem involvement, bilateral pyramidal tract lesions, or psychogenic unresponsiveness. Decorticate (flexor) posturing may occur with lesions of the internal capsule and rostral cerebral peduncle and decerebrate (extensor) posturing with dysfunction or destruction of the midbrain and rostral pons. Decerebrate posturing occurs in the arms accompanied by flaccidity or slight flexor responses in the legs in patients with extensive brainstem damage extending down to the pons at the trigeminal level.

B. Ocular Findings

1. Pupils—Hypothalamic disease processes may lead to unilateral Horner syndrome, while bilateral diencephalic

involvement or destructive pontine lesions may lead to small but reactive pupils. Ipsilateral pupillary dilation with no direct or consensual response to light occurs with compression of the third cranial nerve, eg, with uncal herniation. The pupils are slightly smaller than normal but responsive to light in many metabolic encephalopathies; however, they may be fixed and dilated following overdosage with atropine or scopolamine, and pinpoint (but responsive) with opioids.

2. Corneal reflex—Touching the cornea with a wisp of sterile gauze or cotton should elicit a blink reflex. The afferent limb of the arc is mediated by the fifth cranial nerve; the efferent limb by the seventh nerve. A unilateral absent corneal reflex implies damage to the ipsilateral pons or a trigeminal deficit. Bilateral loss can be seen with large pontine lesions or in deep pharmacologic coma.

3. Eye movements—Conjugate deviation of the eyes to the side suggests the presence of an ipsilateral hemispheric lesion, a contralateral pontine lesion, or ongoing seizures from the contralateral hemisphere. A mesencephalic lesion leads to downward conjugate deviation. Dysconjugate ocular deviation in coma implies a structural brainstem lesion unless there was preexisting strabismus.

The oculomotor responses to passive head turning and to caloric stimulation relate to each other and provide complementary information. In response to brisk rotation of the head from side to side and to flexion and extension of the head, normally conscious patients with open eyes do not exhibit contraversive conjugate eye deviation (**oculocephalic reflex**) unless there is voluntary visual fixation or bilateral frontal pathology. With cortical depression in lightly comatose patients, a brisk oculocephalic reflex is seen. With brainstem lesions, this oculocephalic reflex becomes impaired or lost, depending on the site of the lesion.

The **oculovestibular reflex** is tested by caloric stimulation using irrigation with ice water. In normal patients, jerk nystagmus is elicited for about 2 or 3 minutes, with the slow component toward the irrigated ear. In unconscious patients with an intact brainstem, the fast component of the nystagmus disappears, so that the eyes tonically deviate toward the irrigated side for 2–3 minutes before returning to their original position. With impairment of brainstem function, the response becomes abnormal and finally disappears. In metabolic coma, oculocephalic and oculovestibular reflex responses are preserved, at least initially.

C. Respiratory Patterns

Diseases causing coma may lead to respiratory abnormalities. **Cheyne-Stokes respiration** (in which episodes of deep breathing alternate with periods of apnea) may occur with bihemispheric or diencephalic disease or in metabolic disorders. **Central neurogenic hyperventilation** occurs with lesions of the brainstem tegmentum; **apneustic breathing** (in which there are prominent end-inspiratory pauses) suggests damage at the pontine level (eg, due to basilar artery occlusion); and **ataxic breathing** (a completely irregular pattern of breathing with deep and shallow breaths occurring randomly) is associated with lesions of the lower pontine tegmentum and medulla.

1. Stupor & Coma Due to Structural Lesions

Supratentorial mass lesions tend to affect brain function in a systematic way. There may initially be signs of hemispheric dysfunction, such as hemiparesis. As coma develops and deepens, cerebral function becomes progressively disturbed, producing a predictable progression of neurologic signs that suggest rostrocaudal deterioration.

Thus, as a supratentorial mass lesion begins to impair the diencephalon, the patient becomes drowsy, then stuporous, and finally comatose. There may be Cheyne-Stokes respiration; small but reactive pupils or an ipsilateral third nerve palsy due to uncal herniation; normal oculocephalic responses with side-to-side head movements but sometimes an impairment of reflex upward gaze with brisk flexion of the head; tonic ipsilateral deviation of the eyes in response to vestibular stimulation with cold water; and initially a positive response to pain but subsequently only decorticate posturing. With further progression, midbrain failure occurs. Motor dysfunction progresses from decorticate to bilateral decerebrate posturing in response to painful stimuli; Cheyne-Stokes respiration is gradually replaced by sustained central hyperventilation; the pupils become middle-sized and fixed; and the oculocephalic and oculovestibular reflex responses become impaired, abnormal, or lost. As the pons and then the medulla fail, the pupils remain unresponsive; oculovestibular responses are unobtainable; respiration is rapid and shallow; and painful stimuli may lead only to flexor responses in the legs. Finally, respiration becomes irregular and stops, the pupils often then dilating widely.

In contrast, a **subtentorial (ie, brainstem) lesion** may lead to an early, sometimes abrupt disturbance of consciousness without any orderly rostrocaudal progression of neurologic signs. Compressive lesions of the brainstem, especially cerebellar hemorrhage, may be clinically indistinguishable from intraparenchymal processes.

A structural lesion is suspected if the findings suggest focality. In such circumstances, a CT scan should be performed before, or instead of, a lumbar puncture in order to avoid any risk of cerebral herniation. Further management is of the causal lesion and is considered separately under the individual disorders.

2. Stupor & Coma Due to Metabolic Disturbances

Patients with a metabolic cause of coma generally have signs of patchy, diffuse, and symmetric neurologic involvement that cannot be explained by loss of function at any single level or in a sequential manner, although focal or lateralized deficits may occur in hypoglycemia. Pupillary reactivity is usually preserved. Comatose patients with meningitis, encephalitis, or subarachnoid hemorrhage may also exhibit little in the way of focal neurologic signs, however, and clinical evidence of meningeal irritation is sometimes very subtle in comatose patients. Examination of the cerebrospinal fluid in such patients is essential to establish the correct diagnosis.

In patients with coma due to cerebral ischemia and hypoxia, the absence of pupillary light reflexes 24 hours

after return of spontaneous circulation indicates that there is little chance of regaining independence; absent corneal reflexes or absent or extensor motor responses at 72 hours also indicate a grim prognosis. Physical findings are less reliable predictors of outcome among those treated with therapeutic hypothermia, although absent corneal or pupillary light reflexes at 72 hours likely indicate a poor prognosis, as do bilaterally absent cortical somatosensory evoked potentials in response to median nerve stimulation after the patient has returned to normothermia.

Treatment of metabolic encephalopathy is of the underlying disturbance and is considered in other chapters. If the cause of the encephalopathy is obscure, all medications except essential ones may have to be withdrawn in case they are responsible for the altered mental status.

3. Brain Death

Brain death occurs when there is complete and irreversible cessation of all brain function; although the organs can be maintained with mechanical ventilation for the purposes of donation, in most countries the diagnosis of brain death is *equivalent to a declaration of death*. To diagnose brain death, the cause of coma must be established, be compatible with a known cause of brain death, and be irreversible. Reversible coma simulating brain death may be seen with hypothermia (temperature lower than 32°C) and overdose with central nervous system depressant drugs. These conditions must be excluded by warming the patient and allowing enough time for all sedating medications to be metabolized (ie, at least five half-lives) or by measuring serum levels. Severe blood pressure, electrolyte, acid-base, and endocrine derangements cannot be present.

Finally, a neurologic examination must demonstrate that the patient is comatose (ie, no eye opening and no response to central or peripheral pain); has lost all brain-stem reflex responses, including the pupillary, corneal, oculovestibular, oculocephalic, oropharyngeal, and cough reflexes; and has no respiratory drive. The response to pain should be absent or only consist of spinal reflex movements; decerebrate or decorticate posturing is not consistent with brain death. Absence of respiratory drive is demonstrated with an **apnea test** (absence of spontaneous respiratory activity at a PaCO_2 of at least 60 mm Hg or after a rise of 20 mm Hg from baseline).

Certain ancillary tests may assist the determination of brain death if an apnea test cannot be performed but are not essential. These include an isoelectric electroencephalogram, when the recording is made according to the recommendations of the American Clinical Neurophysiology Society, and demonstration of an absent cerebral circulation by intravenous radioisotope cerebral angiography or by four-vessel contrast cerebral angiography.

4. Persistent Vegetative State

Patients with severe bilateral hemispheric disease may show some improvement from an initially comatose state, so that, after a variable interval, they appear to be awake but lie motionless and without evidence of awareness or higher mental activity. This is called a “**persistent**”

vegetative state once it has lasted over 4 weeks and has also been variously referred to as akinetic mutism, apallic state, or coma vigil. Patients in a vegetative state from a medical cause (eg, anoxic brain injury) for more than 3 months and from a traumatic brain injury for more than 12 months are said to be in a “**chronic**” vegetative state, from which a few patients may regain consciousness but remain severely disabled.

5. Minimally Conscious State

In this state, patients exhibit inconsistent evidence of consciousness. There is some degree of functional recovery of behaviors suggesting self- or environmental-awareness, such as basic verbalization or context-appropriate gestures, emotional responses (eg, smiling) to emotional but not neutral stimuli, or purposive responses to environmental stimuli (eg, a finger movement or eye blink apparently to command). Further improvement is manifest by the restoration of communication with the patient. The minimally conscious state may be temporary or permanent. Little information is available about its natural history or long-term outlook, which reflects the underlying cause. The likelihood of useful functional recovery diminishes with time; after 12 months, patients are likely to remain severely disabled and without a reliable means of communication. Prognostication is difficult. Amantadine (100–200 mg orally daily) may hasten recovery when given to patients in a vegetative or minimally conscious state 4–16 weeks after traumatic brain injury.

6. Locked-In Syndrome (De-Efferented State)

Acute destructive lesions (eg, infarction, hemorrhage, demyelination, encephalitis) involving the ventral pons and sparing the tegmentum may lead to a mute, quadriparetic but conscious state in which the patient is capable of blinking and voluntary eye movement in the vertical plane, with preserved pupillary responses to light. Such a patient can mistakenly be regarded as comatose. Clinicians should recognize that “locked-in” individuals are fully aware of their surroundings. The prognosis is usually poor, but recovery has occasionally been reported in some cases, including resumption of independent daily life. A similar condition may occur with severe Guillain-Barré syndrome and has a better prognosis.

Giacino JT et al. Practice guideline update recommendations summary: disorders of consciousness: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology; the American Congress of Rehabilitation Medicine; and the National Institute on Disability, Independent Living, and Rehabilitation Research. Neurology. 2018;91:450. [PMID: 30089618]

HEAD INJURY

Trauma is the most common cause of death in young people, and head injury accounts for almost half of these trauma-related deaths. Head injury severity ranges from **concussion** to **severe traumatic brain injury (TBI)**. Concussion is broadly defined as an alteration in mental status

Table 24–7. Glasgow Coma Scale.¹

Points	Eye Opening	Verbal Response	Motor Response
1	None	None	None
2	To pain	Vocal but not verbal	Extension
3	To voice	Verbal but not conversational	Flexion
4	Spontaneous	Conversational but disoriented	Withdraws from pain
5	Spontaneous	Oriented	Localizes pain
6	Spontaneous	Oriented	Obeys commands

¹GCS score indicating severity of traumatic brain injury (TBI): mild, 13–15; moderate, 9–12; severe, ≤ 8.

Reproduced, with permission, from Aminoff MJ et al. *Clinical Neurology*, 9th ed, McGraw-Hill Education, 2015; Data from Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet*. 1974;304:81–4.

caused by trauma with or without loss of consciousness. The term concussion is often used synonymously with mild TBI. Grades of TBI are traditionally defined by the Glasgow Coma Scale (GCS) measured 30 minutes after injury (Table 24–7).

Head trauma may cause cerebral injury through a variety of mechanisms (Table 24–8). Central to management is determination of which patients need head imaging and observation. Of particular concern is identification of patients with epidural and subdural hematoma, who may present with normal neurologic findings shortly after injury (**lucid interval**) but rapidly deteriorate thereafter, and in whom surgical intervention is life-saving.

► Clinical Findings

A. Symptoms and Signs

Common symptoms of concussion that develop acutely include headache, nausea, vomiting, confusion, disorientation, dizziness, and imbalance. A period of amnesia encompassing the traumatic event and a variable period of time leading up to the trauma is typical. Loss of consciousness may occur. Additional symptoms of photophobia, phonophobia, difficulty concentrating, irritability, and sleep and mood disturbances may develop over the following hours to days. Examination is usually normal, although orientation and attention, short-term memory, and reaction time may be impaired. Persistent or progressive decline in the level of consciousness after the initial injury, or focal neurologic findings, suggests the need for urgent imaging and neurosurgical consultation.

Patients should also be examined for signs of scalp lacerations, facial and skull fracture, and neck injury. The clinical signs of basilar skull fracture include bruising

Table 24–8. Acute cerebral sequelae of head injury (listed in alphabetical order).

Sequelae	Clinical Features	Pathology
Acute epidural hemorrhage	Headache, confusion, somnolence, seizures, and focal deficits occur several hours after injury (lucid interval) and lead to coma, respiratory depression, and death unless treated by surgical evacuation.	Tear in meningeal artery, vein, or dural sinus, leading to hematoma visible on CT scan.
Acute subdural hemorrhage	Similar to epidural hemorrhage, but interval before onset of symptoms is longer. Neurosurgical consultation for consideration of evacuation.	Hematoma from tear in veins from cortex to superior sagittal sinus or from cerebral laceration, visible on CT scan.
Cerebral contusion or laceration	Loss of consciousness longer than with concussion. Focal neurologic deficits are often present. May lead to death or severe residual neurologic deficit.	Bruising on side of impact (coup injury) or contralaterally (contrecoup injury). Vasogenic edema, multiple petechial hemorrhages, and mass effect. May have subarachnoid bleeding. Herniation may occur in severe cases. Cerebral laceration specifically involves tearing of the cerebral tissue and pia-arachnoid overlying a contusion.
Cerebral hemorrhage	Generally develops immediately after injury. Clinically resembles hypertensive hemorrhage. Surgery to relieve mass effect is sometimes necessary.	Hematoma, visible on CT scan.
Concussion	A transient, trauma-induced alteration in mental status that may or may not involve loss of consciousness. Symptoms and signs include headache, nausea, disorientation, irritability, amnesia, clumsiness, visual disturbances, and focal neurologic deficit.	Unknown; likely mild diffuse axonal injury and excitotoxic neuronal injury. Cerebral contusion may occur.
Diffuse axonal injury	Persistent loss of consciousness, coma, or persistent vegetative state resulting from severe rotational shearing forces or deceleration.	Imaging may be normal or may show tiny, scattered white matter hemorrhages. Histology reveals torn axons.

about the orbit (**raccoon sign**), blood in the external auditory meatus (**Battle sign**), and leakage of cerebrospinal fluid (which can be identified by its glucose or beta-2-transferrin content) from the ear or nose. Cranial nerve palsies (involving especially the first, second, third, fourth, fifth, seventh, and eighth nerves in any combination) may also occur. The head and neck should be immobilized until imaging can be performed.

B. Imaging and Other Investigations

Current recommendations are that head CT be performed in patients with concussion and any of the following: GCS score less than 15, focal neurologic deficit, seizure, coagulopathy, aged 65 or older, skull fracture, persistent headache or vomiting, retrograde amnesia exceeding 30 minutes, intoxication, or soft tissue injury of the head or neck. Otherwise, patients can be sent home as long as a responsible caregiver can check the patient at hourly intervals for the next 24 hours. Patients requiring imaging should be admitted unless the head CT is normal, the GCS score is 15, there have been no seizures, there is no predisposition to bleeding, and they can be monitored by a caregiver at home.

Because injury to the spine may have accompanied head trauma, cervical spine radiographs (three views) or CT should always be obtained in comatose patients and in patients with severe neck pain or a deficit possibly related to cord compression.

Treatment

Head injury can often be prevented by helmets, seatbelts, and other protective equipment.

After intracranial bleeding has been excluded clinically or by head CT, treatment of mild TBI is aimed at promoting resolution of postconcussive symptoms and *preventing recurrent injury*, which increases the risk of chronic neurobehavioral impairment and delays recovery. Rarely, a recurrent concussion while a patient is still symptomatic from a first concussion may lead to fatal cerebral edema (**second impact syndrome**). These observations form the basis of the recommendation that patients at risk for recurrent concussion (eg, athletes) be held out of the risky activity until their concussive symptoms have fully resolved.

In patients hospitalized with moderate or severe TBI, management often requires a multidisciplinary approach due to multiple concomitant injuries. Elevated intracranial pressure can result from diffuse axonal injury or a hematoma requiring surgical evacuation, or from a variety of medical causes. Decompressive craniectomy may reduce otherwise refractory intracranial hypertension but does not improve neurologic outcome. Hypothermia is associated with worsened functional outcomes.

Because bridging veins between the brain and venous sinuses become more vulnerable to shear injury as the brain atrophies, a **subdural hematoma** may develop days or weeks following head injury in elderly patients or even occur spontaneously. Clinical presentation can be subtle, often with mental changes such as slowness, drowsiness, headache, confusion, or memory disturbance. Focal

neurologic deficits such as hemiparesis or hemisensory disturbance are less common. Surgical intervention is indicated if the hematoma is 10 mm or more in thickness or there is a midline shift of 5 mm or more; if there is a decline in GCS score of 2 or more from injury to hospital admission; or if one or both pupils are fixed and dilated.

Scalp lacerations and depressed skull fractures should be treated surgically as appropriate. Simple skull fractures require no specific treatment. If there is any leakage of cerebrospinal fluid, conservative treatment, with elevation of the head, restriction of fluids, and administration of acetazolamide (250 mg orally four times daily), is often helpful; if the leak continues for more than a few days, lumbar subarachnoid drainage may be necessary. Antibiotics are given if infection occurs, based on culture and sensitivity studies; vaccination against pneumococcus is recommended (see Table 30-7). Only very occasional patients require intracranial repair of the dural defect because of persistence of the leak or recurrent meningitis.

Prognosis

Moderate and severe TBI may result in permanent cognitive and motor impairment depending on the severity and location of the initial injury. Initial GCS and head CT findings have prognostic value. Among patients with a GCS score of 8 or less at presentation, mortality approaches 30% and only one-third of survivors regain functional independence. Cognitive impairment tends to affect frontal and temporal lobe function, causing deficits in attention, memory, judgment, and executive function. Behavioral dysregulation, depression, and disinhibition can impair social functioning. Anosmia, presumably due to shearing of fibers from the nasal epithelium, is common.

Epilepsy can develop after TBI, especially with more severe injury. Among patients with severe TBI (typically loss of consciousness for at least 12–24 hours, intracranial hematoma, depressed skull fracture, or cerebral contusion), phenytoin or levetiracetam is typically given for 7 days to reduce the incidence of early posttraumatic seizures; this is done exclusively to minimize acute complications resulting from such seizures and does not prevent the development of posttraumatic epilepsy.

Among patients with mild TBI, symptoms of concussion resolve in most patients by 1 month and in the vast majority by 3 months. Prolonged postconcussive symptoms are uncommon, persisting at 1 year in 10–15% of patients. Risk factors for prolonged postconcussive symptoms include active litigation regarding the injury; repeated concussions; and GCS score of 13 or less at presentation. Headaches often have migrainous features and may respond to tricyclic antidepressants or beta-blockers (see Table 24-1). Opioids should be avoided to minimize the risk of medication overuse headache. Mood symptoms may respond to antidepressants, anxiolytics, and cognitive behavioral therapy.

There appears to be an association between head trauma and the later development of neurodegenerative disease, such as Alzheimer disease, Parkinson disease, or amyotrophic lateral sclerosis (ALS). Normal pressure hydrocephalus may also occur. Repetitive, mild head

injury, such as that which occurs in athletes or military personnel, can lead to **chronic traumatic encephalopathy**, a distinct pathologic entity associated with mood and cognitive changes and characterized by the abnormal aggregation of tau or other proteins either focally or globally in the cerebral cortex. Whether chronic traumatic encephalopathy is a static response to recurrent head injury or a progressive neurodegenerative disease is not known, but the severity of neuropathology appears to correlate to lifetime exposure to repetitive head injury.

► When to Refer

- Patients with focal neurologic deficits, altered consciousness, or skull fracture.
- Patients with late complications of head injury, eg, posttraumatic seizure disorder or normal pressure hydrocephalus.

► When to Admit

- Patients with concussion and GCS score less than 15, predisposition to bleeding, seizure, or no responsible caregiver at home.
- Patients with abnormal head CT.

Mariani M et al. Clinical presentation of chronic traumatic encephalopathy. Semin Neurol. 2020;40:370. [PMID: 32740900]
Misch MR et al. Sports medicine update: concussion. Emerg Med Clin North Am. 2020;38:207. [PMID: 31757251]

MULTIPLE SCLEROSIS



ESSENTIALS OF DIAGNOSIS

- ▶ Episodic neurologic symptoms.
- ▶ Patient usually < 55 years of age at onset.
- ▶ Single pathologic lesion cannot explain clinical findings.
- ▶ Multiple foci best visualized by MRI.

► General Considerations

This common neurologic disorder, which probably has an autoimmune basis, has its greatest incidence in young adults. Epidemiologic studies indicate that multiple sclerosis is much more common in persons of western European lineage who live in temperate zones. No population with a high risk for multiple sclerosis exists between latitudes 40° N and 40° S. A genetic susceptibility to the disease is present. Pathologically, focal—often perivenular—areas of demyelination with reactive gliosis are found scattered in the white matter of the brain and spinal cord and in the optic nerves. Axonal damage also occurs.

► Clinical Findings

A. Symptoms and Signs

The common initial presentation is weakness, numbness, tingling, or unsteadiness in a limb; spastic paraparesis; retrobulbar optic neuritis; diplopia; dysequilibrium; or a sphincter disturbance such as urinary urgency or hesitancy. Symptoms may disappear after a few days or weeks, although examination often reveals a residual deficit.

Several forms of the disease are recognized. In most patients, there is an interval of months or years after the initial episode before new symptoms develop or the original ones recur (**relapsing-remitting disease**). Eventually, however, relapses and usually incomplete remissions lead to increasing disability, with weakness, spasticity, and ataxia of the limbs, impaired vision, and urinary incontinence. The findings on examination at this stage commonly include optic atrophy; nystagmus; dysarthria; and pyramidal, sensory, or cerebellar deficits in some or all of the limbs. In some of these patients, the clinical course changes so that a steady deterioration occurs, unrelated to acute relapses (**secondary progressive disease**). Less commonly, symptoms are steadily progressive from their onset, and disability develops at a relatively early stage (**primary progressive disease**). The diagnosis cannot be made with confidence unless the total clinical picture indicates involvement of *different parts of the central nervous system at different times*. Fatigue is common in all forms of the disease.

A number of factors (eg, infection) may precipitate or trigger exacerbations. Relapses are reduced in pregnancy but are more likely during the 2 or 3 months following pregnancy, possibly because of the increased demands and stresses that occur in the postpartum period.

B. Imaging

MRI of the brain and cervical cord has a major role in excluding other causes of neurologic dysfunction and in demonstrating the presence of multiple lesions. In T1-weighted images, hypointense “black holes” probably represent areas of permanent axonal damage. Gadolinium-enhanced T1-weighted images may highlight areas of active inflammation with breakdown of the blood-brain barrier, which helps identify newer lesions. T2-weighted images provide information about disease burden or total number of lesions, which typically appear as areas of high signal intensity. CT scans are less helpful than MRI.

In patients with myelopathy alone and no clinical or laboratory evidence of more widespread disease, MRI or myelography is necessary to exclude a congenital or acquired surgically treatable lesion. In patients with mixed pyramidal and cerebellar deficits in the limbs, the foramen magnum region must be visualized to exclude the possibility of Arnold-Chiari malformation, in which parts of the cerebellum and lower brainstem are displaced into the cervical canal.

C. Laboratory and Other Studies

A definitive diagnosis can never be based solely on the laboratory findings. If there is clinical evidence of only a

single lesion in the central nervous system, multiple sclerosis cannot properly be diagnosed unless it can be shown that other regions are affected subclinically. Visual, brain-stem auditory, and somatosensory evoked potentials are helpful in this regard, but other disorders may also be characterized by multifocal electrophysiologic abnormalities reflecting disease of central white matter. Certain infections (eg, HIV, Lyme disease, syphilis), connective tissue diseases (eg, systemic lupus erythematosus, Sjögren syndrome), sarcoidosis, metabolic disorders (eg, vitamin B₁₂ deficiency), and lymphoma may therefore require exclusion.

There may be mild lymphocytosis or a slightly increased protein concentration in the cerebrospinal fluid, especially soon after an acute relapse. Elevated IgG in cerebrospinal fluid and discrete bands of IgG (oligoclonal bands) are present in many patients. The presence of such bands is not specific, however, since they have been found in a variety of inflammatory neurologic disorders and occasionally in patients with vascular or neoplastic disorders of the nervous system.

Vitamin D deficiency may be associated with an increased risk of developing multiple sclerosis; randomized trials have not shown vitamin D supplementation reduces attack rate or progression in relapsing remitting disease.

D. Diagnosis

Multiple sclerosis should not be diagnosed unless there is evidence that two or more different regions of the central white matter (*dissemination in space*) have been affected at different times (*dissemination in time*); the most widely used diagnostic algorithm is the 2017 revision to the McDonald criteria. The diagnosis may be made in a patient with two or more typical attacks and objective evidence on clinical examination of two lesions (eg, optic disk atrophy and pyramidal weakness), or objective evidence of one lesion with clear-cut historical evidence the other attack was typical of multiple sclerosis and in a distinct neuroanatomic location, and when no alternative explanation for the patient's presentation has been found. To fulfill the criterion of dissemination in space in a patient with two clinical attacks but objective clinical evidence of only one lesion, MRI should demonstrate at least one lesion in at least two of four typical sites (periventricular, cortical or juxtacortical, infratentorial, or spinal); alternatively, an additional attack localized to a different site suffices. The criterion of dissemination in time in a patient with only one attack can be fulfilled by the simultaneous presence of gadolinium-enhancing and nonenhancing lesions at any time (including at initial examination); the presence of oligoclonal bands unique to the cerebrospinal fluid; a new lesion on follow-up MRI; or a second attack. Lesions in the optic nerve on MRI in patients with optic neuritis cannot be used to fulfill the McDonald criteria for dissemination in space or time. Primary progressive disease requires at least a year of progression, plus two of three of the following: at least one typical brain lesion, at least two spinal lesions, or oligoclonal banding in the cerebrospinal fluid.

In patients with a single clinical event who do not satisfy criteria for multiple sclerosis, a diagnosis of a **clinically isolated syndrome (CIS)** is made. Such patients are at risk for developing multiple sclerosis and are sometimes offered beta-interferon or glatiramer acetate therapy, which may delay progression to clinically definite disease. Follow-up MRI should be considered 6–12 months later to assess for the presence of any new lesion.

Treatment

At least partial recovery from acute exacerbations can reasonably be expected, but further relapses may occur without warning. Some disability is likely to result eventually, but about half of all patients are without significant disability even 10 years after onset of symptoms. Current treatments are chiefly aimed at preventing relapses, thereby reducing disability.

Recovery from acute relapses may be hastened by treatment with corticosteroids, but the extent of recovery is unchanged. Intravenous therapy is often given first—typically methylprednisolone 1 g daily for 3 days—followed by oral prednisone at 60–80 mg daily for 1 week with a taper over the ensuing 2–3 weeks, but randomized trials show similar efficacy whether the initial high dose is given orally or intravenously. Long-term treatment with corticosteroids provides no benefit and does not prevent further relapses. Transient exacerbation of symptoms relating to intercurrent infection or heat requires no added treatment.

In patients with relapsing disease, numerous medications have well-established efficacy at *reducing the frequency of attacks* (Table 24–9). The initial agent is chosen after considering medication tolerance and risks, patient preference, and disease severity. Glatiramer acetate, an interferon, or dimethyl fumarate is often used initially due to favorable side effect profiles and availability, although the efficacy of early treatment with higher intensity therapy is being explored. In general, the medications most effective in reducing relapses have stronger immunomodulatory effects and more, albeit rare, serious adverse effects. Prescription of these agents should be managed by a specialist.

Ocrelizumab is the only medication effective in slowing disability progression in primary progressive multiple sclerosis and is approved for this indication by the FDA. For patients with active secondary progressive disease, cladribine, ocrelizumab, ofatumumab, ozanimod, and siponimod can be used. Plasmapheresis is sometimes helpful in patients with severe relapses unresponsive to corticosteroids.

Symptomatic therapy for spasticity, neurogenic bladder, or fatigue may be required. Fatigue is especially common in multiple sclerosis, and modafinil (200 mg orally every morning) is an effective and FDA-approved therapy for this indication. Dalfampridine (an extended-release formulation of 4-aminopyridine administered as 10 mg orally twice daily) is efficacious at improving timed gait in multiple sclerosis. Depression and even suicidality can occur in multiple sclerosis and may worsen with interferon beta-1a therapy; screening and conventional treatment of such symptoms are appropriate.

Table 24–9. Treatment of multiple sclerosis (in alphabetical order within categories).¹

Medication	Dose
Acute Episode, Including Relapse²	
Dexamethasone	160 mg orally daily for 3–5 days
Methylprednisolone	1 g intravenously or orally daily for 3–5 days
Plasmapheresis	
Disease-Modifying Therapy (FDA approved)	
Alemtuzumab (Lemtrada) ^{3,4}	12 mg intravenously daily for 5 days; 3-day course given 1 year later
Cladribine (Mavenclad) ^{3,5,6}	1.75 mg/kg orally divided between weeks 1 and 5, repeated once in 1 year
Dimethyl fumarate (Tecfidera) ^{3,5}	240 mg orally twice daily
Fingolimod (Gilenya) ^{3,4,5}	0.5 mg orally daily
Glatiramer acetate (Copaxone, Mylan, Glatopa) ⁵	20 mg subcutaneously daily or 40 mg subcutaneously three times weekly
Interferon β-1a (Rebif) ⁵	44 mcg subcutaneously three times per week
Interferon β-1a (Avonex) ⁵	30 mcg intramuscularly once per week
Interferon β-1b (Betaseron, Extavia) ⁵	0.25 mg subcutaneously on alternate days
Mitoxantrone ³	12 mg/m ² intravenously every 3 months; maximum lifetime dose, 140 mg/m ²
Natalizumab (Tysabri) ^{3,4}	300 mg intravenously monthly
Ocrelizumab (Ocrevus) ^{3,4,5,6,7}	300 mg intravenously on day 1 and day 15, followed by 600 mg every 6 months
Ofatumumab (Kesimpta) ^{3,4,5,6}	20 mg subcutaneously weeks 0, 1, 2, 4, and monthly thereafter
Ozanimod (Zeposia) ^{3,4,5,6}	0.23 mg orally daily on days 1–4, 0.46 mg daily on days 5–7, and 0.92 mg daily thereafter
Pegylated interferon β-1a (Plegridy) ⁵	125 mg subcutaneously once every 2 weeks
Siponimod (Mayzent) ^{3,4,5,6}	0.25 mg orally daily, titrated over 5 or 6 days to 1 or 2 mg orally daily, depending on CYP2C9 genotype
Teriflunomide (Aubagio) ⁵	14 mg or 7 mg orally daily

¹Several of these agents require special monitoring or pretreatment; some should be avoided during pregnancy. Readers should refer to the manufacturer's guidelines.

²For corticosteroid-refractory relapses, plasmapheresis may be used.

³Relapse prevention for disease activity despite use of first-line treatment.

⁴High disease activity (typically with multiple gadolinium-enhancing lesions on MRI).

⁵Relapse prevention, first-line treatment.

⁶Active secondary progressive disease.

⁷Primary progressive disease.

► When to Refer

All patients, but especially those with progressive disease despite standard therapy, should be referred.

► When to Admit

- Patients requiring plasma exchange for severe relapses unresponsive to corticosteroids.
- During severe relapses.
- Patients unable to manage at home.

Freedman MS et al. Treatment optimization in multiple sclerosis: Canadian MS working group recommendations. *Can J Neurol Sci.* 2020;47:437. [PMID: 32654681]

Rae-Grant A et al. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology.* 2018;90:777. [PMID: 29686116]

NEUROMYELITIS OPTICA

This disorder is characterized by optic neuritis and acute myelitis with MRI changes that extend over at least three segments of the spinal cord. An isolated myelitis or optic neuritis may also occur. Previously known as Devic disease and once regarded as a variant of multiple sclerosis, neuromyelitis optica is associated with a specific antibody marker (NMO-IgG) targeting the water channel aquaporin-4 in 80% of cases, and with antibodies to myelin oligodendrocyte glycoprotein (MOG-IgG) in approximately 33% of NMO-IgG seronegative patients. MRI of the brain typically does not show widespread white matter involvement, but such changes do not exclude the diagnosis. Treatment is by long-term immunosuppression. Three medications are approved by the FDA for treatment of neuromyelitis optica based on placebo-controlled trials demonstrating a reduced annual relapse rate or time to first relapse. Eculizumab is a complement inhibitor, inebilizumab is a humanized

anti-CD19 antibody that depletes B cells, and satralizumab is an interleukin-6 receptor antagonist. Use of eculizumab requires prior immunization against meningococcus. Off-label therapy is with rituximab (two 1-g intravenous infusions spaced by 2 weeks, or four weekly infusions of 375 mg/m²; re-dosing may occur every 6 months or when CD19/20-positive or CD27-positive lymphocytes become detectable), mycophenolate mofetil (500–1500 mg orally twice daily, titrated until the absolute lymphocyte count falls below 1500/mcL [$1.5 \times 10^9/\text{L}$]), or azathioprine (2.5–3 mg/kg orally). Acute relapses are treated with corticosteroids at doses similar to those outlined for multiple sclerosis and with plasma exchange for severe relapses unresponsive to corticosteroids.

Cree BAC et al; N-MOmentum Study Investigators. Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): a double-blind, randomized placebo-controlled phase 2/3 trial. Lancet. 2019;394:1352. [PMID: 31495497]

Pittock SJ et al. Eculizumab in aquaporin-4-positive neuromyelitis optica spectrum disorder. N Engl J Med. 2019;381:614. [PMID: 31050279]

VITAMIN E DEFICIENCY

Vitamin E deficiency may produce a disorder somewhat similar to Friedreich ataxia. There is spinocerebellar degeneration involving particularly the posterior columns of the spinal cord and leading to limb ataxia, sensory loss, absent tendon reflexes, slurring of speech, and, in some cases, pigmentary retinal degeneration. The disorder may occur as a consequence of malabsorption or on a hereditary basis (eg, abetalipoproteinemia).

SPASTICITY

The term “spasticity” is commonly used for an upper motor neuron deficit, but it properly refers to a velocity-dependent increase in resistance to passive movement that affects different muscles to a different extent, is not uniform in degree throughout the range of a particular movement, and is commonly associated with other features of pyramidal deficit. It is often a major complication of stroke, cerebral or spinal injury, static perinatal encephalopathy, and multiple sclerosis. Spasticity may be exacerbated by pressure injuries, urinary or other infections, and nociceptive stimuli.

Physical therapy with appropriate stretching programs is important during rehabilitation after the development of an upper motor neuron lesion and in subsequent management of the patient. The aim is to prevent joint and muscle contractures and perhaps to modulate spasticity.

Medication management is important also, but treatment may increase functional disability when increased extensor tone is providing additional support for patients with weak legs. Pharmacologic treatment with baclofen (5–10 mg twice daily orally titrated to 80 mg daily), tizanidine (2–8 mg three times daily orally), diazepam (2–10 mg three times daily orally), or dantrolene (25 mg once daily orally, titrated every 3 days as tolerated to a maximum of

100 mg four times daily) is often helpful. Dantrolene is best avoided in patients with poor respiratory function or severe myocardial disease. Cannabinoids are also effective in reducing spasticity, but are associated with side effects, including dizziness, drowsiness, and fatigue. Intramuscular injection of botulinum toxin is used to relax targeted muscles.

In patients with severe spasticity that is unresponsive to other therapies and is associated with marked disability, intrathecal injection of phenol or alcohol may be helpful. Surgical options include implantation of an intrathecal baclofen pump, rhizotomy, or neurectomy. Severe contractures may be treated by surgical tendon release.

MYELOPATHIES IN AIDS

A variety of myopathies may occur in patients with AIDS. These are discussed in Chapter 31.

MYELOPATHY OF HUMAN T-CELL LEUKEMIA VIRUS INFECTION

Human T-cell leukemia virus (HTLV-1), a human retrovirus, is transmitted by breastfeeding, sexual contact, blood transfusion, and contaminated needles. Most patients are asymptomatic, but after a variable latent period (which may be as long as several years), a myopathy develops in some instances. The MRI, electrophysiologic, and cerebrospinal fluid findings are similar to those of multiple sclerosis, but HTLV-1 antibodies are present in serum and spinal fluid. There is no specific treatment, but intravenous or oral corticosteroids may help in the initial inflammatory phase of the disease. Prophylactic measures are important. Needles or syringes should not be shared; infected patients should not breastfeed their infants or donate blood, semen, or other tissue. Infected patients should use condoms to prevent sexual transmission.

SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD

Subacute combined degeneration of the spinal cord is due to **vitamin B₁₂ deficiency**, such as occurs in pernicious anemia. It is characterized by myopathy with spasticity, weakness, proprioceptive loss, and numbness due to degeneration of the corticospinal tracts and posterior columns. Polyneuropathy, mental changes, or optic neuropathy also develop in some patients. Megaloblastic anemia may also occur, but this does *not* parallel the neurologic disorder, and the former may be obscured if folic acid supplements have been taken. Treatment is with vitamin B₁₂. For pernicious anemia, a convenient therapeutic regimen is 1000 mcg cyanocobalamin intramuscularly daily for 1 week, then weekly for 1 month, and then monthly for the remainder of the patient's life. Oral cyanocobalamin replacement is not advised for pernicious anemia when neurologic symptoms are present. A similar syndrome is caused by recreational abuse of inhaled nitrous oxide due to its interference with vitamin B₁₂ metabolism. Copper deficiency, caused by malabsorption or excess zinc ingestion, may also be responsible.

SPINAL TRAUMA



ESSENTIALS OF DIAGNOSIS

- ▶ History of preceding trauma.
- ▶ Development of acute neurologic deficit.
- ▶ Signs of myelopathy on examination.

General Considerations

While spinal cord damage may result from whiplash injury, severe injury usually relates to fracture-dislocation causing compression or angular deformity of the cord either cervically or in the lower thoracic and upper lumbar regions. Extreme hypotension following injury may also lead to cord infarction.

Clinical Findings

Total cord transection results in immediate flaccid paralysis and loss of sensation below the level of the lesion. Reflex activity is lost for a variable period, and there is urinary and fecal retention. As reflex function returns over the following days and weeks, spastic paraparesis or quadriplegia develops, with hyperreflexia and extensor plantar responses, but a flaccid atrophic (lower motor neuron) paralysis may be found depending on the segments of the cord that are affected. The bladder and bowels also regain some reflex function, permitting urine and feces to be expelled at intervals. As spasticity increases, flexor or extensor spasms (or both) of the legs become troublesome, especially if the patient develops bed sores or a urinary tract infection. Paraparesis with the legs in flexion or extension may eventually result.

With lesser degrees of injury, patients may be left with mild limb weakness, distal sensory disturbance, or both. Sphincter function may also be impaired, urinary urgency and urge incontinence being especially common. More particularly, a unilateral cord lesion leads to an ipsilateral motor disturbance with accompanying impairment of proprioception and contralateral loss of pain and temperature appreciation below the lesion (**Brown-Séquard syndrome**). A central cord syndrome may lead to a lower motor neuron deficit at the level of the lesion and loss of pain and temperature appreciation below it, with sparing of posterior column functions. With more extensive involvement, posterior column sensation may also be impaired and pyramidal weakness develops. A radicular deficit may occur at the level of the injury—or, if the cauda equina is involved, there may be evidence of disturbed function in several lumbosacral roots.

Treatment

Treatment of the injury consists of immobilization and—if there is cord compression—early decompressive laminectomy and fusion (within 24 hours). Early treatment with high doses of corticosteroids (eg, methylprednisolone,

30 mg/kg by intravenous bolus, followed by 5.4 mg/kg/h for 23 hours) may improve neurologic recovery if commenced within 8 hours after injury, although the evidence is limited and some neurosurgical guidelines do not recommend their use. Anatomic realignment of the spinal cord by traction and other orthopedic procedures is important. Subsequent care of the residual neurologic deficit—paraplegia or quadriplegia—requires treatment of spasticity and care of the skin, bladder, and bowels.

When to Refer

All patients with focal neurologic deficits should be referred.

When to Admit

- Patients with neurologic deficits.
- Patients with spinal cord injury, compression, or acute epidural or subdural hematoma.
- Patients with vertebral fracture-dislocation likely to compress the cord.

Ong B et al. Management of the patient with chronic spinal cord injury. *Med Clin North Am.* 2020;104:263. [PMID: 32035568]

SYRINGOMYELIA

Destruction or degeneration of gray and white matter adjacent to the central canal of the cervical spinal cord leads to cavitation and accumulation of fluid within the spinal cord. The precise pathogenesis is unclear, but many cases are associated with **Arnold-Chiari malformation**, in which there is displacement of the cerebellar tonsils, medulla, and fourth ventricle into the spinal canal, sometimes with accompanying meningocele. In such circumstances, the cord cavity connects with and may merely represent a dilated central canal. In other cases, the cause of cavitation is less clear. There is a characteristic clinical picture, with segmental atrophy, areflexia, and loss of pain and temperature appreciation in a “cape” distribution, owing to the destruction of fibers crossing in front of the central canal in the mid-cervical spinal cord. Thoracic kyphoscoliosis is usually present. With progression, involvement of the long motor and sensory tracts occurs as well, so that a pyramidal and sensory deficit develops in the legs. Upward extension of the cavitation (syringobulbia) leads to dysfunction of the lower brainstem and thus to bulbar palsy, nystagmus, and sensory impairment over one or both sides of the face.

Syringomyelia, ie, cord cavitation, may also occur in association with an intramedullary tumor or following severe cord injury, and the cavity then does not communicate with the central canal.

In patients with Arnold-Chiari malformation, CT scans reveal a small posterior fossa and enlargement of the foramen magnum, along with other associated skeletal abnormalities at the base of the skull and upper cervical spine. MRI reveals the syrinx as well as the characteristic findings of the Arnold-Chiari malformation, including the caudal displacement of the fourth ventricle and herniation of the

cerebellar tonsils through the foramen magnum. Focal cord enlargement is found at myelography or by MRI in patients with cavitation related to past injury or intramedullary neoplasms.

Treatment of Arnold-Chiari malformation with associated syringomyelia is by suboccipital craniectomy and upper cervical laminectomy, with the aim of decompressing the malformation at the foramen magnum. The cord cavity should be drained and, if necessary, an outlet for the fourth ventricle can be made. In cavitation associated with intramedullary tumor, treatment is surgical, but radiation therapy may be necessary if complete removal is not possible. Posttraumatic syringomyelia is also treated surgically if it leads to increasing neurologic deficits or to intolerable pain.

DEGENERATIVE MOTOR NEURON DISEASES



ESSENTIALS OF DIAGNOSIS

- ▶ Weakness.
- ▶ No sensory loss or sphincter disturbance.
- ▶ Progressive course.
- ▶ No identifiable underlying cause other than genetic basis in familial cases.

► General Considerations

This group of degenerative disorders is characterized clinically by weakness and variable wasting of affected muscles, without accompanying sensory changes.

Motor neuron disease in adults generally commences between 30 and 60 years of age. There is degeneration of the anterior horn cells in the spinal cord, the motor nuclei of the lower cranial nerves, and the corticospinal and corticobulbar pathways. The disorder is usually sporadic, but familial cases may occur and several genetic mutations or loci have been identified. Cigarette smoking may be one risk factor.

► Classification

Five varieties have been distinguished on clinical grounds.

A. Progressive Bulbar Palsy

Bulbar involvement predominates owing to disease processes affecting primarily the motor nuclei of the cranial nerves.

B. Pseudobulbar Palsy

Bulbar involvement predominates in this variety also, but it is due to bilateral corticobulbar disease and thus reflects upper motor neuron dysfunction. There may be a “pseudobulbar affect,” with uncontrollable episodes of laughing or crying to stimuli that would not normally have elicited such marked reactions.

C. Progressive Spinal Muscular Atrophy

This is characterized primarily by a lower motor neuron deficit in the limbs due to degeneration of the anterior horn cells in the spinal cord.

D. Primary Lateral Sclerosis

There is a purely upper motor neuron deficit in the limbs.

E. Amyotrophic Lateral Sclerosis (ALS)

A mixed upper and lower motor neuron deficit is found in the limbs. This disorder is sometimes associated with cognitive decline (in a pattern consistent with frontotemporal dementia), a pseudobulbar affect, or parkinsonism. Approximately 10% of ALS cases are familial and have been associated with mutations at several different genetic loci, including a hexanucleotide repeat on chromosome 9 that also associates with frontotemporal dementia.

► Differential Diagnosis

The spinal muscular atrophies (SMAs) are inherited syndromes caused most often by mutations of the survival motor neuron 1 (*SMN1*) gene on chromosome 5. Different mutations result in more or less severe disruptions of the protein, resulting in an age of onset that ranges from infancy (SMA type I), to early (type II) or late childhood (type III), to adulthood (type IV). X-linked spinal and bulbar muscular atrophy (Kennedy syndrome) is associated with an expanded trinucleotide repeat sequence on the androgen receptor gene and carries a more benign prognosis than other forms of motor neuron disease.

There are reports of juvenile SMA due to hexosaminidase deficiency. Pure motor syndromes resembling motor neuron disease may also occur in association with monoclonal gammopathy or multifocal motor neuropathies with conduction block. A motor neuronopathy may also develop in Hodgkin disease and has a relatively benign prognosis. Infective anterior horn cell diseases (polio virus or West Nile virus infection) can generally be distinguished by the acute onset and monophasic course of the illness, as discussed in Chapter 32. Acute flaccid myelitis following infection with enterovirus may occur, especially in children, without sensory involvement and resembles poliomyelitis. There is no specific treatment.

► Clinical Findings

A. Symptoms and Signs

Difficulty in swallowing, chewing, coughing, breathing, and talking (dysarthria) occurs with bulbar involvement. In progressive bulbar palsy, there is drooping of the palate; a depressed gag reflex; pooling of saliva in the pharynx; a weak cough; and a wasted, fasciculating tongue. In pseudobulbar palsy, the tongue is contracted and spastic and cannot be moved rapidly from side to side. Limb involvement is characterized by motor disturbances (weakness, stiffness, wasting, fasciculations) reflecting lower or upper

motor neuron dysfunction; there are no objective changes on sensory examination, although there may be vague sensory complaints. The sphincters are generally spared. Cognitive changes or pseudobulbar affect may be present. The disorder is progressive, and ALS is usually fatal within 3–5 years; death usually results from pulmonary infections. Patients with bulbar involvement generally have the poorest prognosis, while patients with primary lateral sclerosis often have a longer survival despite profound quadriplegia and spasticity.

B. Laboratory and Other Studies

Electromyography may show signs of acute and chronic partial denervation with reinnervation. In patients with suspected ALS, the diagnosis should not be made with confidence unless such changes are found in at least three spinal regions (cervical, thoracic, lumbosacral) or two spinal regions and the bulbar musculature. Motor conduction velocity is usually normal but may be slightly reduced, and sensory conduction studies are also normal. Biopsy of a wasted muscle shows the histologic changes of denervation but is not necessary for diagnosis. The serum creatine kinase may be slightly elevated but never reaches the extremely high values seen in some of the muscular dystrophies. The cerebrospinal fluid is normal. To diagnose SMA, molecular genetic testing for pathogenic variants of *SMN1* is available. There are abnormal findings on rectal biopsy and reduced hexosaminidase A in serum and leukocytes in patients with juvenile SMA due to hexosaminidase deficiency.

Treatment

Riluzole, 50 mg orally twice daily, which reduces the pre-synaptic release of glutamate, increased short-term survival in ALS in randomized trials. Edaravone, a free radical scavenger, slows disease progression in patients with mild disease. It is administered in monthly cycles as a 60 mg intravenous infusion on days 1–14 in the first month and days 1–10 in the subsequent months.

Noninvasive ventilation at least 4 hours per day in patients with a maximal inspiratory pressure less than 60 cm H₂O may prolong survival in ALS. Symptomatic and supportive measures to treat spasticity (discussed earlier), drooling, and dysphagia, prevent contractures, and preserve mobility are important. Drooling is treated with over-the-counter decongestants, anticholinergic medications (such as trihexyphenidyl, amitriptyline, or atropine), botulinum toxin injections into the salivary glands, or use of a portable suction machine. Physical and occupational therapy are helpful throughout the disease course. Combination dextromethorphan/quinidine (20 mg/10 mg, one tablet orally once or twice daily) may relieve symptoms of pseudobulbar affect. A semiliquid diet or gastrostomy tube feeding may be needed if dysphagia is severe; it is advisable to perform the procedure before the forced vital capacity falls below 50% of predicted to minimize the risk of complications. Tracheostomy is sometimes performed if respiratory muscles are severely affected; however, in the terminal stages of these disorders, realistic expectations

and advance care planning should be discussed. Information on palliative care is provided in Chapter 5.

Treatment of spinal muscular atrophy takes advantage of the fact that the SMN protein is also encoded by a second gene, *SMN2*, that usually does not translate functional protein due to aberrant splicing. Nusinersen is an antisense oligonucleotide that modulates pre-messenger RNA splicing of the *SMN2* gene and results in increased production of the full-length protein; it has shown effectiveness in both infants and children with SMA. It is approved for use in all ages and is administered intrathecally (12 mg every 14 days for three doses, then once after a 30-day interval, then once every 4 months). Risdiplam (5 mg orally daily for patients 2 years of age and older weighing more than 20 kg) is a small molecule *SMN2* splicing modifier that also results in production of the full-length protein and is approved for use in infants and adults. Gene therapy with intravenous delivery of an intact *SMN1* gene using a viral vector (onasemnogene abeparvovec) improves ventilator-free survival compared to historical controls and is approved by the FDA for use in children under 2 years of age with bi-allelic mutations in *SMN1*.

When to Refer

All patients (to exclude other treatable causes of symptoms and signs) should be referred.

When to Admit

Patients may need to be admitted for initiation or titration of noninvasive ventilation, or for periods of increased requirement of noninvasive ventilator support during pulmonary infections.

Mercuri E et al; CHERISH Study Group. Nusinersen versus sham control in later-onset spinal muscular atrophy. *N Engl J Med*. 2018;378:625. [PMID: 29443664]

Norris SP et al. Amyotrophic lateral sclerosis: update on clinical management. *Curr Opin Neurol*. 2020;33:641. [PMID: 32868602]

PERIPHERAL NEUROPATHIES

Peripheral neuropathies can be categorized on the basis of the structure primarily affected. The predominant pathologic feature may be **axonal degeneration (axonal or neuronal neuropathies)** or **paranodal or segmental demyelination**. The distinction may be possible on the basis of neurophysiologic findings. Motor and sensory conduction velocity can be measured in accessible segments of peripheral nerves. In axonal neuropathies, conduction velocity is normal or reduced only mildly and needle electromyography provides evidence of denervation in affected muscles. In demyelinating neuropathies, conduction may be slowed considerably in affected fibers, and in more severe cases, conduction is blocked completely, without accompanying electromyographic signs of denervation.

POLYNEUROPATHIES & MONONEURITIS MULTIPLEX



ESSENTIALS OF DIAGNOSIS

- ▶ Weakness, sensory disturbances, or both in the extremities.
- ▶ Pain is common.
- ▶ Depressed or absent tendon reflexes.
- ▶ May be family history of neuropathy.
- ▶ May be history of systemic illness or toxic exposure.

► General Considerations

Diffuse **polyneuropathies** lead to a symmetric sensory, motor, or mixed deficit, often most marked distally. They include the hereditary, metabolic, and toxic disorders; idiopathic inflammatory polyneuropathy (**Guillain-Barré syndrome**); and the peripheral neuropathies that may occur as a nonmetastatic complication of malignant diseases. Involvement of motor fibers leads to flaccid weakness that is most marked distally; dysfunction of sensory fibers causes impaired sensory perception. Tendon reflexes are depressed or absent. Paresthesias, pain, and muscle tenderness may also occur. Multiple mononeuropathies (**mononeuropathy multiplex**) suggest a patchy multifocal disease process such as vasculopathy (eg, diabetes, arteritis), an infiltrative process (eg, leprosy, sarcoidosis), radiation damage, or an immunologic disorder (eg, brachial plexopathy).

► Clinical Findings

The cause of polyneuropathy or mononeuritis multiplex is suggested by the history, mode of onset, and predominant clinical manifestations. Laboratory workup includes a complete blood count, serum protein electrophoresis with reflex to immunofixation or immunotyping, determination of plasma urea and electrolytes, liver biochemical tests, thyroid function tests, vitamin B₁₂ level, tests for rheumatoid factor and antinuclear antibody, HBsAg determination, a serologic test for syphilis, fasting blood glucose level and hemoglobin A_{1c}, urinary heavy metal levels, cerebrospinal fluid examination, and chest radiography. These tests should be ordered selectively, as guided by symptoms and signs. Measurement of nerve conduction velocity can confirm the peripheral nerve origin of symptoms and provides a means of following clinical changes, as well as indicate the likely disease process (ie, axonal or demyelinating neuropathy). Cutaneous nerve biopsy may help establish a precise diagnosis (eg, polyarteritis, amyloidosis). In about half of cases, no specific cause can be established; of these, slightly less than half are subsequently found to be familial.

► Treatment

Treatment is of the underlying cause, when feasible, and is discussed below under the individual disorders. Physical therapy helps prevent contractures, and splints can

maintain a weak extremity in a position of useful function. Anesthetic extremities must be protected from injury. To guard against burns, patients should check the temperature of water and hot surfaces with a portion of skin having normal sensation, measure water temperature with a thermometer, and use cold water for washing or lower the temperature setting of their hot-water heaters. Shoes should be examined frequently during the day for grit or foreign objects in order to prevent pressure lesions.

Patients with polyneuropathies or mononeuritis multiplex are subject to additional nerve injury at pressure points and should therefore avoid such behavior as leaning on elbows or sitting with crossed legs for lengthy periods.

Neuropathic, burning pain may respond to simple analgesics, such as aspirin or nonsteroidal anti-inflammatory agents, and to gabapentin (300 mg orally three times daily, titrated up to a maximum of 1200 mg orally three times daily as necessary) or pregabalin (50–100 mg orally three times daily). Duloxetine (60 mg orally once or twice daily), venlafaxine (start 37.5 mg orally twice daily, and titrate up to 75 mg orally two to three times daily), or tricyclic antidepressants (eg, amitriptyline 10–150 mg orally at bedtime daily) may be helpful, especially in painful diabetic neuropathy. Medical cannabis may provide some relief, but long-term safety data are lacking. The use of a frame or cradle to reduce contact with bedclothes may be helpful. Many patients experience episodic stabbing pains, which may respond to gabapentin, pregabalin, carbamazepine (start 100 mg orally twice daily, and titrate up to 400 mg orally twice daily), or tricyclic antidepressants. Opioids may be necessary for severe hyperpathia or pain induced by minimal stimuli, but their use generally should be avoided.

Symptoms of autonomic dysfunction are occasionally troublesome. Treatment of postural hypotension is discussed earlier in this chapter. Erectile dysfunction can be treated with phosphodiesterase inhibitors; a flaccid neurologic bladder may respond to parasympathomimetic medications such as bethanechol chloride, 10–50 mg three or four times daily.

Adams D et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N Engl J Med.* 2018;379:11. [PMID: 29972753]

Benson MD et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. *N Engl J Med.* 2018;379:22. [PMID: 29972757]

1. Inherited Neuropathies

A. Charcot-Marie-Tooth Disease (HMSN Type I, II)

There are several distinct varieties of Charcot-Marie-Tooth disease, usually with an autosomal dominant mode of inheritance, but occasional cases occur on a sporadic, recessive, or X-linked basis. Clinical presentation may be with foot deformities or gait disturbances in childhood or early adult life. Slow progression leads to the typical features of polyneuropathy, with distal weakness and wasting that begin in the legs, a variable amount of distal sensory loss, and depressed or absent tendon reflexes. Tremor is a conspicuous feature in some instances. **Hereditary motor**

and sensory neuropathy (HMSN) type I is characterized by demyelination on electrodiagnostic studies and is usually caused by mutations in the peripheral myelin protein 22 or myelin protein zero gene. In **HMSN type II**, electrodiagnostic studies show axonal loss rather than demyelination; one-third of cases are due to mutations in the gene mitofusin 2.

A similar disorder may occur in patients with progressive distal spinal muscular atrophies, but there is no sensory loss; electrophysiologic investigation reveals that motor conduction velocity is normal or only slightly reduced, and nerve action potentials are normal.

B. Dejerine-Sottas Disease (HMSN Type III)

The disorder may occur on a sporadic, autosomal dominant or, less commonly, autosomal recessive basis. Onset in infancy or childhood leads to a progressive motor and sensory polyneuropathy with weakness, ataxia, sensory loss, and depressed or absent tendon reflexes. The peripheral nerves may be palpably enlarged and are characterized pathologically by segmental demyelination, Schwann cell hyperplasia, and thin myelin sheaths. Electrophysiologically, there is a slowing of conduction, and sensory action potentials may be unrecordable.

C. Friedreich Ataxia

This disorder, the only known **autosomal recessive trinucleotide repeat disease**, is caused by expansion of a poly-GAA locus in the gene for frataxin on chromosome 9, leading to symptoms in childhood or early adult life. The gait becomes ataxic, the hands become clumsy, and other signs of cerebellar dysfunction develop accompanied by weakness of the legs and extensor plantar responses. Involvement of peripheral sensory fibers leads to sensory disturbances in the limbs and depressed tendon reflexes. There is bilateral pes cavus. Pathologically, there is a marked loss of cells in the posterior root ganglia and degeneration of peripheral sensory fibers. In the central nervous system, changes are conspicuous in the posterior and lateral columns of the cord. Electrophysiologically, conduction velocity in motor fibers is normal or only mildly reduced, but sensory action potentials are small or absent. Cardiac disease is the most common cause of death.

In the differential diagnosis for Friedreich ataxia are other spinocerebellar ataxias, a growing group of at least 30 inherited disorders, each involving a different identified gene. These heterogeneous disorders, which frequently (but not exclusively) exhibit an autosomal dominant inheritance pattern and poly-CAG expansion of the affected gene, typically cause cerebellar ataxia and varying combinations of other symptoms (such as peripheral neuropathy, ophthalmoparesis, dysarthria, and pyramidal and extrapyramidal signs).

D. Refsum Disease (HMSN Type IV)

This autosomal recessive disorder is due to a disturbance in phytanic acid metabolism. Pigmentary retinal degeneration is accompanied by progressive sensorimotor polyneuropathy and cerebellar signs. Auditory dysfunction,

cardiomyopathy, and cutaneous manifestations may also occur. Motor and sensory conduction velocities are reduced, often markedly, and there may be electromyographic evidence of denervation in affected muscles. Dietary restriction of phytanic acid and its precursors may be helpful therapeutically. Plasmapheresis to reduce stored phytanic acid may help at the initiation of treatment.

E. Porphyria

Peripheral nerve involvement may occur during acute attacks in both **variegate porphyria** and **acute intermittent porphyria**. Motor symptoms usually occur first, and weakness is often most marked proximally and in the upper limbs rather than the lower. Sensory symptoms and signs may be proximal or distal in distribution. Autonomic involvement is sometimes pronounced. The electrophysiologic findings are in keeping with the results of neuropathologic studies suggesting that the neuropathy is axonal in type (see Chapter 40).

F. Familial Amyloid Polyneuropathy

Sensory and autonomic symptoms are especially conspicuous, whereas distal wasting and weakness occur later. The polyneuropathy is axonal and likely results from amyloid deposition within the peripheral nerves due to mutations in the genes encoding transthyretin, apolipoprotein A1, or gelsolin. **Transthyretin amyloidosis** is the most common; it is associated with cardiomyopathy, nephropathy, leptomeningeal involvement, and vitreous opacity; and is treatable with liver transplantation, the small interfering ribonucleic acid patisiran (0.3 mg/kg up to 30 mg intravenously once every 3 weeks), or the antisense oligonucleotide inotersen (284 mg subcutaneously weekly). Tafamidis helps transthyretin amyloid cardiomyopathy and may slow the progression of the neuropathy.

2. Neuropathies Associated with Systemic & Metabolic Disorders

A. Diabetes Mellitus

In this disorder, involvement of the peripheral nervous system may lead to symmetric sensory or mixed polyneuropathy, asymmetric motor radiculoneuropathy or plexopathy (diabetic amyotrophy), thoracoabdominal radiculopathy, autonomic neuropathy, or isolated lesions of individual nerves. These may occur singly or in any combination and are discussed in Chapter 27.

B. Uremia

Uremia may lead to a symmetric sensorimotor polyneuropathy that tends to affect the lower limbs more than the upper limbs and is more marked distally than proximally (see Chapter 22). The diagnosis can be confirmed electrophysiologically because motor and sensory conduction velocity is moderately reduced. The neuropathy improves both clinically and electrophysiologically with kidney transplantation and to a lesser extent with chronic dialysis.

C. Alcoholism and Nutritional Deficiency

Many patients with alcohol use disorder have an axonal distal sensorimotor polyneuropathy that is frequently accompanied by painful cramps, muscle tenderness, and painful paresthesias and is often more marked in the legs than in the arms. Symptoms of autonomic dysfunction may also be conspicuous. Motor and sensory conduction velocity may be slightly reduced, even in subclinical cases, but gross slowing of conduction is uncommon. Treatment is similar to diabetic polyneuropathy but also includes abstinence from alcohol. A similar distal sensorimotor polyneuropathy is a well-recognized feature of **beriberi** (thiamine deficiency). In vitamin B₁₂ deficiency, distal sensory polyneuropathy may develop but is usually overshadowed by central nervous system manifestations (eg, myelopathy, optic neuropathy, or intellectual changes).

D. Paraproteinemias

A symmetric sensorimotor polyneuropathy that is gradual in onset, progressive in course, and often accompanied by pain and dysesthesias in the limbs may occur in patients (especially men) with **plasma cell myeloma** (formerly multiple myeloma). The neuropathy is of the axonal type in classic lytic myeloma, but segmental demyelination (primary or secondary) and axonal loss may occur in sclerotic myeloma and lead to predominantly motor clinical manifestations. Both demyelinating and axonal neuropathies are also observed in patients with paraproteinemias without myeloma. A small fraction will develop myeloma if serially followed. The demyelinating neuropathy in these patients may be due to the monoclonal proteins reacting to a component of the nerve myelin. The neuropathy of classic plasma cell myeloma is poorly responsive to therapy. The polyneuropathy of **benign monoclonal gammopathy** may respond to immunosuppressant medications and plasmapheresis.

Polyneuropathy may also occur in association with monoclonal gammopathy of unknown significance, macroglobulinemia, and cryoglobulinemia and sometimes responds to plasmapheresis. Many patients with an IgM M-protein will have antibodies to myelin-associated glycoprotein (MAG); these patients may respond to treatment with rituximab. Entrapment neuropathy, such as carpal tunnel syndrome, is more common than polyneuropathy in patients with (nonhereditary) generalized amyloidosis.

3. Neuropathies Associated with Infectious & Inflammatory Diseases

A. Leprosy

Leprosy is an important cause of peripheral neuropathy in certain parts of the world. Sensory disturbances are mainly due to involvement of intracutaneous nerves. In tuberculous leprosy, they develop at the same time and in the same distribution as the nerve; trunks lying beneath the lesion are also involved. In lepromatous leprosy, there is more extensive sensory loss, and this develops earlier and to a greater extent in the coolest regions of the body, such as the dorsal surfaces of the hands and feet, where the bacilli

proliferate most actively. Motor deficits result from involvement of superficial nerves where their temperature is lowest, eg, the ulnar nerve in the region proximal to the olecranon groove, the median nerve as it emerges from beneath the forearm flexor muscle to run toward the carpal tunnel, the peroneal nerve at the head of the fibula, and the posterior tibial nerve in the lower part of the leg; patchy facial muscular weakness may also occur owing to involvement of the superficial branches of the seventh cranial nerve.

Motor disturbances in leprosy are suggestive of multiple mononeuropathy, whereas sensory changes resemble those of distal polyneuropathy. Examination, however, relates the distribution of sensory deficits to the temperature of the tissues; in the legs, for example, sparing frequently occurs between the toes and in the popliteal fossae, where the temperature is higher. Treatment is with antileprotic agents (see Chapter 33).

B. AIDS

A variety of neuropathies occur in HIV-infected patients (see Chapter 31).

C. Lyme Borreliosis

The neurologic manifestations of Lyme disease include meningitis, meningoencephalitis, polyradiculoneuropathy, mononeuropathy multiplex, and cranial neuropathy. Serologic tests establish the underlying disorder. Lyme disease and its treatment are discussed in depth in Chapter 34.

D. Sarcoidosis

Cranial nerve palsies (especially facial palsy), multiple mononeuropathy and, less commonly, symmetric polyneuropathy may all occur, the latter sometimes preferentially affecting either motor or sensory fibers. Improvement may occur with use of corticosteroids.

E. Polyarteritis

Involvement of the vasa nervorum by the vasculitic process may result in infarction of the nerve. Clinically, one encounters an asymmetric sensorimotor polyneuropathy (mononeuritis multiplex) that pursues a waxing and waning course. Corticosteroids and cytotoxic agents—especially cyclophosphamide—may be of benefit in severe cases (Chapter 20).

F. Rheumatoid Arthritis

Compressive or entrapment neuropathies, ischemic neuropathies, mild distal sensory polyneuropathy, and severe progressive sensorimotor polyneuropathy can occur in rheumatoid arthritis.

4. Neuropathy Associated with Critical Illness

Patients in intensive care units with sepsis and multiorgan failure sometimes develop polyneuropathies. This may be manifested initially by unexpected difficulty in weaning

patients from a mechanical ventilator and in more advanced cases by wasting and weakness of the extremities and loss of tendon reflexes. Sensory abnormalities are relatively inconspicuous. The neuropathy is axonal in type. Its pathogenesis is obscure, and treatment is supportive. The prognosis is good provided patients recover from the underlying critical illness. A myopathy may also occur (discussed below).

5. Toxic Neuropathies

Axonal polyneuropathy may follow exposure to industrial agents or pesticides such as acrylamide, organophosphorus compounds, hexacarbon solvents, methyl bromide, and carbon disulfide; metals such as arsenic, thallium, mercury, and lead; and medications such as phenytoin, amiodarone, perhexiline, isoniazid, nitrofurantoin, vincristine, and pyridoxine in high doses. Detailed occupational, environmental, and medical histories and recognition of clusters of cases are important in suggesting the diagnosis. Treatment is by preventing further exposure to the causal agent. Isoniazid neuropathy is prevented by pyridoxine supplementation.

Diphtheritic neuropathy results from a neurotoxin released by the causative organism and is common in many areas. Palatal weakness may develop 2–4 weeks after infection of the throat, and infection of the skin may similarly be followed by focal weakness of neighboring muscles. Disturbances of accommodation may occur about 4–5 weeks after infection and distal sensorimotor demyelinating polyneuropathy after 1–3 months.

6. Neuropathies Associated with Malignant Diseases

A variety of neuropathies have been associated with non-metastatic complications of malignancy and were discussed earlier.

7. Acute Idiopathic Polyneuropathy (Guillain-Barré Syndrome)



ESSENTIALS OF DIAGNOSIS

- ▶ Acute or subacute progressive polyradiculoneuropathy.
- ▶ Weakness is more severe than sensory disturbances.
- ▶ Acute dysautonomia may be life-threatening.

► General Considerations

This acute or subacute polyradiculoneuropathy sometimes follows infective illness, inoculations, or surgical procedures. There is an association with preceding *Campylobacter jejuni* enteritis. The disorder probably has an immunologic basis, but the precise mechanism is unclear.

► Clinical Findings

A. Symptoms and Signs

The main complaint is of weakness that varies widely in severity in different patients and often has a proximal emphasis and symmetric distribution. It usually begins in the legs, spreading to a variable extent but frequently involving the arms and often one or both sides of the face. The muscles of respiration or deglutition may also be affected. Sensory symptoms are usually less conspicuous than motor ones, but distal paresthesias and dysesthesias are common, and neuropathic or radicular pain is present in many patients. Autonomic disturbances are also common, may be severe, and are sometimes life-threatening; they include tachycardia, cardiac irregularities, hypotension or hypertension, facial flushing, abnormalities of sweating, pulmonary dysfunction, and impaired sphincter control. The axonal subtypes of the syndrome (**acute motor axonal neuropathy [AMAN]** and **acute motor and sensory axonal neuropathy [AMSAN]**) are caused by antibodies to gangliosides on the axon membrane. The **Miller Fisher syndrome**, another subtype, is characterized by the clinical triad of ophthalmoplegia, ataxia, and areflexia, and is associated with anti-GQ1b antibodies.

B. Laboratory Findings

The cerebrospinal fluid characteristically contains a high protein concentration with a normal cell count, but these changes may take up to 2 weeks to develop; white blood cell counts greater than 50 cells/mcL ($0.05 \times 10^9/L$) should prompt consideration of alternative diagnoses. Electrophysiologic studies may reveal marked abnormalities, which do not necessarily parallel the clinical disorder in their temporal course.

► Differential Diagnosis

When the diagnosis is made, the history and appropriate laboratory studies should exclude the possibility of porphyric, diphtheritic, or toxic (heavy metal, hexacarbon, organophosphate) neuropathies, and of HIV infection. The temporal course excludes other peripheral neuropathies. Poliomyelitis, botulism, and tick paralysis must also be considered as they cause weakness of acute onset. The presence of pyramidal signs, a markedly asymmetric motor deficit, a sharp sensory level, or early sphincter involvement should suggest a focal cord lesion.

► Treatment

Treatment with prednisone is ineffective and may prolong recovery time. Plasmapheresis is of value; it is best performed within the first few days of illness and is particularly useful for clinically severe or rapidly progressive cases or those with ventilatory impairment. IVIG (400 mg/kg/day for 5 days) is equally helpful. Patients should be admitted to intensive care units if their forced vital capacity is declining, and intubation is considered if the forced vital capacity reaches 15 mL/kg, the maximum inspiratory

pressure reaches -30 mm Hg, or dyspnea becomes evident. Declining oxygen saturation is a late indicator of neuromuscular respiratory failure. Respiratory toilet and chest physical therapy help prevent atelectasis. Marked hypotension may respond to volume replacement or pressor agents. Thromboprophylaxis is important.

► Prognosis

Most patients eventually make a good recovery, but this may take many months, and about 20% of patients are left with persisting disability. Approximately 3% of patients with acute idiopathic polyneuropathy have one or more clinically similar relapses, sometimes several years after the initial illness.

► When to Refer

All patients should be referred.

► When to Admit

All patients should be hospitalized until their condition is stable and there is no respiratory compromise.

Malek E et al. Guillain-Barré syndrome. *Semin Neurol*. 2019;39:589. [PMID: 31639842]

8. Chronic Inflammatory Polyneuropathy

Chronic inflammatory demyelinating polyneuropathy, an acquired immunologically mediated disorder, is clinically similar to Guillain-Barré syndrome except that it has a relapsing or steadily progressive course over months or years and that autonomic dysfunction is generally less common. It may present as an exclusively motor disorder or with a mixed sensorimotor disturbance. In the relapsing form, partial recovery may occur after some relapses, but in other instances there is no recovery between exacerbations. Although remission may occur spontaneously with time, the disorder frequently follows a progressive downhill course leading to severe functional disability.

Electrodiagnostic studies show marked slowing of motor and sensory conduction, and focal conduction block. Signs of partial denervation may also be present owing to secondary axonal degeneration. Nerve biopsy may show chronic perivascular inflammatory infiltrates in the endoneurium and epineurium, without accompanying evidence of vasculitis. However, a normal nerve biopsy result or the presence of nonspecific abnormalities does not exclude the diagnosis.

Corticosteroids may arrest or reverse the downhill course. Treatment is usually begun with prednisone, 60–80 mg orally daily, continued for 2–3 months or until a definite response has occurred. If no response has occurred despite 3 months of treatment, a higher dose may be tried. In responsive cases, the dose is gradually tapered, but most patients become corticosteroid-dependent, often requiring prednisone, 20 mg daily on alternate days, on a long-term basis. IVIG can be used in place of, or in addition to corticosteroids, and is best used as the initial treatment in pure

motor syndromes (2 g/kg over 2–5 days followed by 1 g/kg every 3 weeks); a weekly regimen of 0.2–0.4 g/kg of a 20% subcutaneous immunoglobulin solution is an effective alternative but has not been compared directly to corticosteroids or IVIG. When both IVIG and corticosteroids are ineffective, plasma exchange may be worthwhile. Consistent with the notion that the condition is antibody mediated, rituximab has shown promise. Immunosuppressant or immunomodulatory medications (such as azathioprine) may be added when the response to other measures is unsatisfactory or to enable maintenance doses of corticosteroids to be lowered. Symptomatic treatment is also important.

Bunschoten C et al. Progress in diagnosis and treatment of chronic inflammatory demyelinating polyneuropathy. *Lancet Neurol*. 2019;18:784. [PMID: 31076244]

MONONEUROPATHIES



ESSENTIALS OF DIAGNOSIS

- ▶ Focal motor or sensory deficit.
- ▶ Deficit is in territory of an individual peripheral nerve.

An individual nerve may be injured along its course or may be compressed, angulated, or stretched by neighboring anatomic structures, especially at a point where it passes through a narrow space (**entrapment neuropathy**). The relative contributions of mechanical factors and ischemia to the local damage are not clear. With involvement of a sensory or mixed nerve, pain is commonly felt distal to the lesion. Symptoms never develop with some entrapment neuropathies, resolve rapidly and spontaneously in others, and become progressively more disabling and distressing in yet other cases. The precise neurologic deficit depends on the nerve involved. Percussion of the nerve at the site of the lesion may lead to paresthesias in its distal distribution.

Entrapment neuropathy may be the sole manifestation of subclinical polyneuropathy, and this must be borne in mind and excluded by nerve conduction studies. Such studies are also indispensable for the localization of the focal lesion.

In patients with acute compression neuropathy such as may occur in intoxicated individuals (**Saturday night palsy**), no treatment is necessary. Complete recovery generally occurs, usually within 2 months, presumably because the underlying pathology is demyelination. However, axonal degeneration can occur in severe cases, and recovery then takes longer and may never be complete.

In chronic compressive or entrapment neuropathies, avoidance of aggravating factors and correction of any underlying systemic conditions are important. Local infiltration of the region about the nerve with corticosteroids may be of value; in addition, surgical decompression may help if

there is a progressively increasing neurologic deficit or if electrodiagnostic studies show evidence of partial denervation in weak muscles.

Peripheral nerve tumors are uncommon, except in neurofibromatosis type 1, but also give rise to mononeuropathy. This may be distinguishable from entrapment neuropathy only by noting the presence of a mass along the course of the nerve and by demonstrating the precise site of the lesion with appropriate electrophysiologic studies. Treatment of symptomatic lesions is by surgical removal if possible.

1. Carpal Tunnel Syndrome

See Chapter 41.

2. Pronator Teres or Anterior Interosseous Syndrome

The median nerve gives off its motor branch, the anterior interosseous nerve, below the elbow as it descends between the two heads of the pronator teres muscle. A lesion of either nerve may occur in this region, sometimes after trauma or owing to compression from, for example, a fibrous band. With anterior interosseous nerve involvement, there is no sensory loss, and weakness is confined to the pronator quadratus, flexor pollicis longus, and the flexor digitorum profundus to the second and third digits. Weakness is more widespread and sensory changes occur in an appropriate distribution when the median nerve itself is affected. The prognosis is variable. If improvement does not occur spontaneously, decompressive surgery may be helpful.

3. Ulnar Nerve Lesions

Ulnar nerve lesions are likely to occur in the elbow region as the nerve runs behind the medial epicondyle and descends into the cubital tunnel. In the condylar groove, the ulnar nerve is exposed to pressure or trauma. Moreover, any increase in the carrying angle of the elbow, whether congenital, degenerative, or traumatic, may cause excessive stretching of the nerve when the elbow is flexed. Ulnar nerve lesions may also result from thickening or distortion of the anatomic structures forming the cubital tunnel, and the resulting symptoms may also be aggravated by flexion of the elbow, because the tunnel is then narrowed by tightening of its roof or inward bulging of its floor. A severe lesion at either site causes sensory changes in the fifth and medial half of the fourth digits and along the medial border of the hand. There is weakness of the ulnar-innervated muscles in the forearm and hand. With a cubital tunnel lesion, however, there may be relative sparing of the flexor carpi ulnaris muscle. Electrophysiologic evaluation using nerve stimulation techniques allows more precise localization of the lesion.

Initial treatment consists of avoiding pressure on the medial elbow (eg, avoid resting the elbows on arm rests; pad the elbow during sleep) and preventing prolonged elbow flexion, especially at night. Splints are available to keep the elbow from flexing beyond 45 to 90 degrees. If conservative measures are unsuccessful in relieving symptoms and preventing further progression, surgical treatment may be necessary. This consists of nerve transposition

if the lesion is in the condylar groove, or a release procedure if it is in the cubital tunnel.

Ulnar nerve lesions may also develop at the wrist or in the palm of the hand, usually owing to repetitive trauma or to compression from ganglia or benign tumors. They can be subdivided depending on their presumed site. Compressive lesions are treated surgically. If repetitive mechanical trauma is responsible, this is avoided by occupational adjustment or job retraining.

4. Radial Nerve Lesions

The radial nerve is particularly liable to compression or injury in the axilla (eg, by crutches or by pressure when the arm hangs over the back of a chair). This leads to weakness or paralysis of all the muscles supplied by the nerve, including the triceps. Sensory changes may also occur but are often surprisingly inconspicuous, being marked only in a small area on the back of the hand between the thumb and index finger. Injuries to the radial nerve in the spiral groove occur characteristically during deep sleep, as in intoxicated individuals, and there is then sparing of the triceps muscle, which is supplied more proximally. The nerve may also be injured at or above the elbow; its purely motor posterior interosseous branch, supplying the extensors of the wrist and fingers, may be involved immediately below the elbow, but then there is sparing of the extensor carpi radialis longus, so that the wrist can still be extended. The superficial radial nerve may be compressed by handcuffs or a tight watch strap.

5. Femoral Neuropathy

The clinical features of femoral nerve palsy consist of weakness and wasting of the quadriceps muscle, with sensory impairment over the anteromedian aspect of the thigh and sometimes also of the leg to the medial malleolus, and a depressed or absent knee jerk. Isolated femoral neuropathy may occur in patients with diabetes or from compression by retroperitoneal neoplasms or hematomas (eg, expanding aortic aneurysm). Femoral neuropathy may also result from pressure from the inguinal ligament when the thighs are markedly flexed and abducted, as in the lithotomy position.

6. Meralgia Paresthetica

The lateral femoral cutaneous nerve, a sensory nerve arising from the L2 and L3 roots, may be compressed or stretched in obese or diabetic patients and during pregnancy. The nerve usually runs under the outer portion of the inguinal ligament to reach the thigh, but the ligament sometimes splits to enclose it. Hyperextension of the hip or increased lumbar lordosis—such as occurs during pregnancy—leads to nerve compression by the posterior fascicle of the ligament. However, entrapment of the nerve at any point along its course may cause similar symptoms, and several other anatomic variations predispose the nerve to damage when it is stretched. Pain, paresthesia, or numbness occurs about the outer aspect of the thigh, usually unilaterally, and is sometimes relieved by sitting. The pain stops at the knee, unlike the pain from lower lumbar sciatica that radiates to the foot. Examination shows no abnormalities except in

severe cases when cutaneous sensation is impaired in the affected area. Symptoms are usually mild and commonly settle spontaneously. Hydrocortisone injections medial to the anterosuperior iliac spine often relieve symptoms temporarily, while nerve decompression by transposition may provide more lasting relief.

7. Sciatic & Common Peroneal (Fibular) Nerve Palsies

Misplaced deep intramuscular injections are probably still the most common cause of sciatic nerve palsy. Trauma to the buttock, hip, or thigh may also be responsible. The resulting clinical deficit depends on whether the whole nerve has been affected or only certain fibers. In general, the peroneal (fibular) fibers of the sciatic nerve are more susceptible to damage than those destined for the tibial nerve. A sciatic nerve lesion may therefore be difficult to distinguish from peroneal (fibular) neuropathy unless there is electromyographic evidence of involvement of the short head of the biceps femoris muscle. The common peroneal (fibular) nerve itself may be compressed or injured in the region of the head and neck of the fibula, eg, by sitting with crossed legs or wearing high boots. There is weakness of dorsiflexion and eversion of the foot, accompanied by numbness or blunted sensation of the anterolateral aspect of the calf and dorsum of the foot.

8. Tarsal Tunnel Syndrome

The tibial nerve, the other branch of the sciatic, supplies several muscles in the lower extremity, gives origin to the sural nerve, and then continues as the posterior tibial nerve to supply the plantar flexors of the foot and toes. It passes through the tarsal tunnel behind and below the medial malleolus, giving off calcaneal branches and the medial and lateral plantar nerves that supply small muscles of the foot and the skin on the plantar aspect of the foot and toes. Compression of the posterior tibial nerve or its branches between the bony floor and ligamentous roof of the tarsal tunnel leads to pain, paresthesias, and numbness over the bottom of the foot, especially at night, with sparing of the heel. Muscle weakness may be hard to recognize clinically. Compressive lesions of the individual plantar nerves may also occur more distally, with clinical features similar to those of the tarsal tunnel syndrome. Treatment is surgical decompression.

► When to Refer

- If there is uncertainty about the diagnosis.
- Symptoms or signs are progressing despite treatment.

BELL PALSY



ESSENTIALS OF DIAGNOSIS

- Sudden onset of lower motor neuron facial palsy.
- Hyperacusis or impaired taste may occur.
- No other neurologic abnormalities.

► General Considerations

Bell palsy is an *idiopathic facial paresis of lower motor neuron type* that has been attributed to an inflammatory reaction involving the facial nerve near the stylomastoid foramen or in the bony facial canal. In some instances, this may be due to reactivation of herpes simplex or varicella zoster virus infection in the geniculate ganglion. The disorder is more common in pregnant women and in persons with diabetes mellitus.

► Clinical Findings

The facial paresis (Figure 24–1) generally comes on abruptly, but it may worsen over the following day or so. Pain about the ear precedes or accompanies the weakness in many cases but usually lasts for only a few days. The face itself feels stiff and pulled to one side. There may be ipsilateral restriction of eye closure and difficulty with eating and fine facial movements. A disturbance of taste is common, owing to involvement of chorda tympani fibers, and hyperacusis due to involvement of fibers to the stapedius occurs occasionally. In cases due to herpes zoster infection, vesicles may be observed in the external ear canal.

► Differential Diagnosis

Lower motor neuron facial palsy can be differentiated from stroke by clinical examination. A stroke or other central lesion will not cause hyperacusis or disturbance of taste,



▲ **Figure 24–1.** Facial palsy caused by an infection with *Borrelia burgdorferi* (Lyme disease). (Public Health Image Library, CDC.)

generally spares the forehead, and is accompanied by other focal deficits. An isolated facial palsy may occur in patients with HIV seropositivity, sarcoidosis, Lyme disease (Figure 24–1; also see Chapter 34), or any process causing an inflammatory reaction in the subarachnoid space, such as meningitis. Whenever facial palsies occur bilaterally, or a facial palsy occurs in conjunction with other neurologic deficits, MRI brain imaging should be undertaken and other investigations considered.

► Treatment

Approximately 60% of cases of Bell palsy recover completely without treatment, presumably because the lesion is so mild that it leads merely to conduction block. Treatment with corticosteroids (prednisone 60 mg orally daily for 5 days followed by a 5-day taper, or prednisolone 25 mg orally twice daily for 10 days) increases the chance of a complete recovery at 9–12 months by 12–15%. Treatment with acyclovir or valacyclovir is only indicated when there is evidence of herpetic vesicles in the external ear canal. It is helpful to protect the eye with lubricating drops (or lubricating ointment at night) and a patch if eye closure is not possible. There is no evidence that surgical procedures to decompress the facial nerve are of benefit. Physical therapy may improve facial function.

Gagyor I et al. Antiviral treatment of Bell's palsy (idiopathic facial palsy). Cochrane Database Syst Rev. 2019;9:CD001869. [PMID: 31486071]

DISCOGENIC NECK PAIN



ESSENTIALS OF DIAGNOSIS

- ▶ Neck pain, sometimes radiating to arms.
- ▶ Restricted neck movements.
- ▶ Motor, sensory, or reflex changes in arms with root involvement.
- ▶ Neurologic deficit in legs, gait disorder, or sphincter disturbance with cord involvement.

► General Considerations

A variety of congenital abnormalities may involve the cervical spine and lead to neck pain; these include hemivertebrae, fused vertebrae, basilar impression, and instability of the atlantoaxial joint. Traumatic, degenerative, infective, and neoplastic disorders may also lead to pain in the neck. When rheumatoid arthritis involves the spine, it tends to affect especially the cervical region, leading to pain, stiffness, and reduced mobility; displacement of vertebrae or atlantoaxial subluxation may lead to cord compression that can be life-threatening if not treated by fixation. Further

details are given in Chapter 41 and discussion here is restricted to disk disease.

1. Acute Cervical Disk Protrusion

Acute cervical disk protrusion leads to pain in the neck and radicular pain in the arm, exacerbated by head movement. With lateral herniation of the disk, motor, sensory, or reflex changes may be found in a radicular (usually C6 or C7) distribution on the affected side (Figure 24–2); with more centrally directed herniations, the spinal cord may also be involved, leading to spastic paraparesis and sensory disturbances in the legs, sometimes accompanied by impaired sphincter function. The diagnosis is confirmed by MRI or CT myelography. In mild cases, the prognosis is good and complete recovery occurs in a majority of patients with conservative therapy. Evidence does not support any specific intervention, and some combination of bed rest, activity restriction, immobilization of the neck in a collar for several weeks, and physical therapy is generally prescribed. If these measures are unsuccessful or the patient has a significant neurologic deficit, surgical removal of the protruding disk may be necessary.

2. Cervical Spondylosis

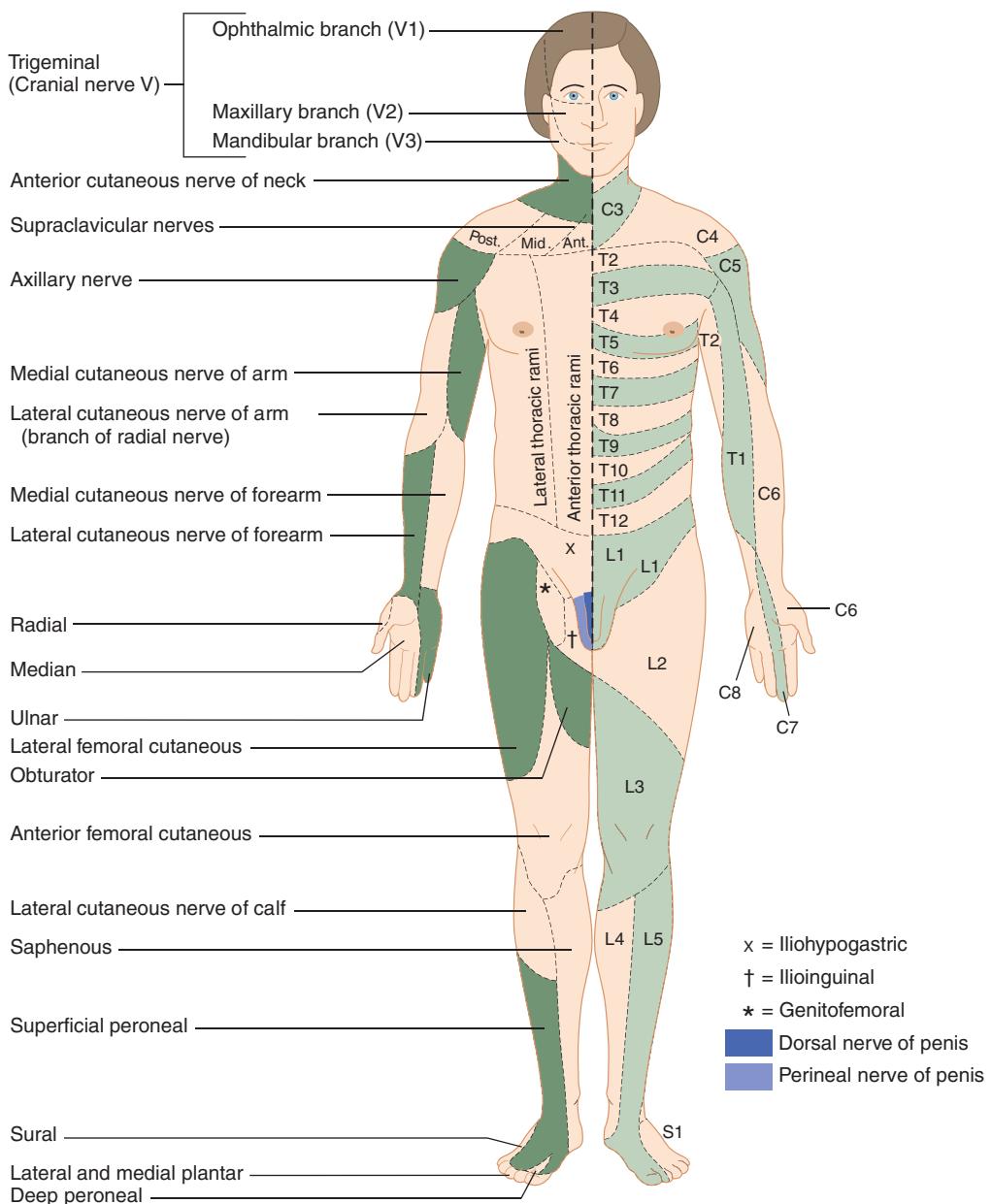
Cervical spondylosis results from chronic cervical disk degeneration, with herniation of disk material, secondary calcification, and associated osteophytic outgrowths. One or more of the cervical nerve roots may be compressed, stretched, or angulated; and myelopathy may also develop as a result of compression, vascular insufficiency, or recurrent minor trauma to the cord. Patients present with neck pain and restricted head movement, occipital headaches, radicular pain and other sensory disturbances in the arms, weakness of the arms or legs, or some combination of these symptoms. Examination generally reveals that lateral flexion and rotation of the neck are limited. A segmental pattern of weakness or dermatomal sensory loss (or both) may be found unilaterally or bilaterally in the upper limbs, and tendon reflexes mediated by the affected root or roots are depressed. The C5 and C6 nerve roots are most commonly involved, and examination frequently then reveals weakness of muscles supplied by these roots (eg, deltoids, supraspinatus and infraspinatus, biceps, brachioradialis), pain or sensory loss about the shoulder and outer border of the arm and forearm, and depressed biceps and brachioradialis reflexes. Spastic paraparesis may also be present if there is an associated myelopathy, sometimes accompanied by urinary urgency, incontinence, or posterior column or spinothalamic sensory deficits in the legs.

Plain radiographs of the cervical spine show osteophyte formation, narrowing of disk spaces, and encroachment on the intervertebral foramina, but such changes are common in middle-aged persons and may be unrelated to the presenting complaint. CT or MRI helps confirm the diagnosis and exclude other structural causes of the myelopathy.

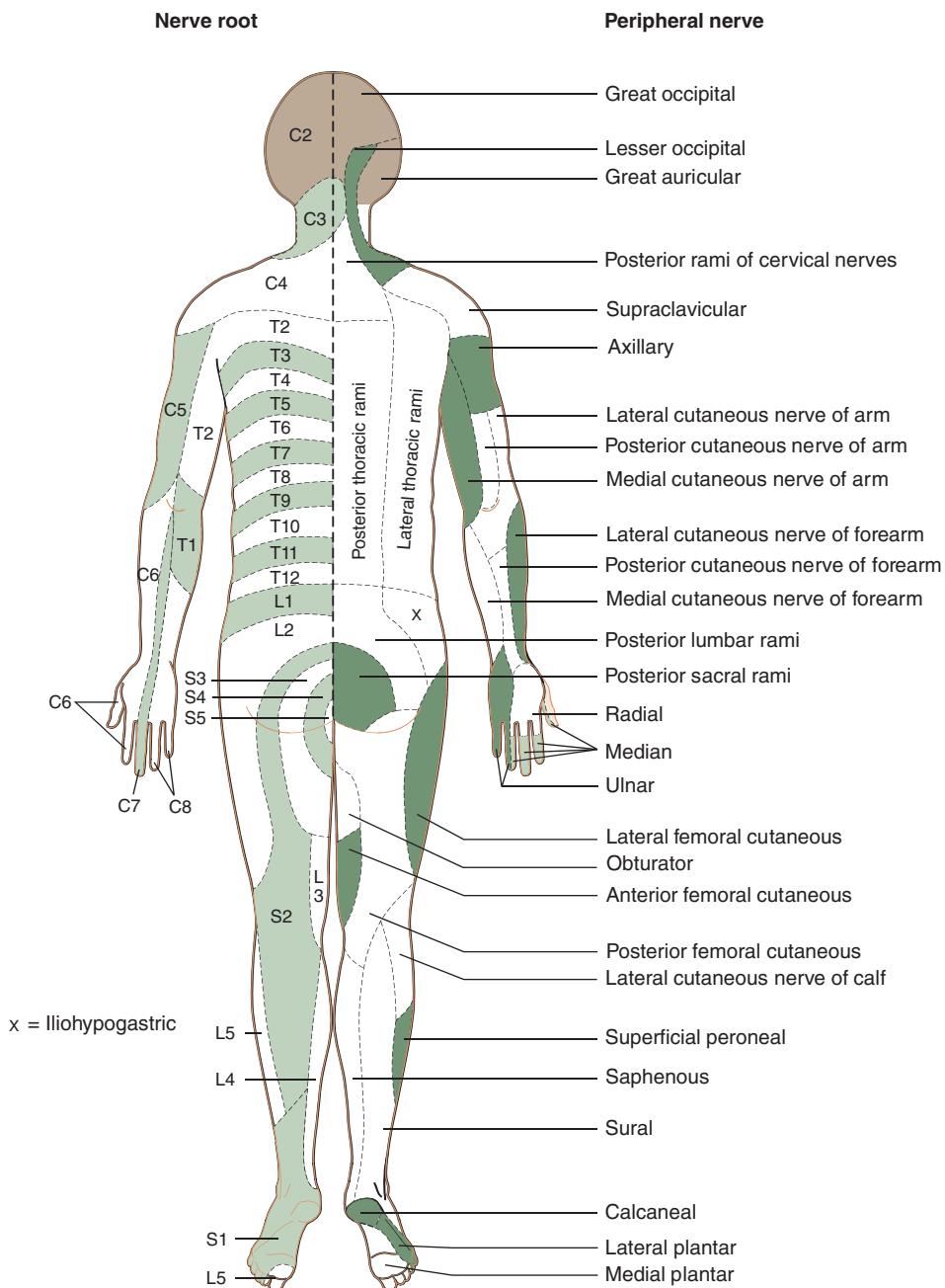
Restriction of neck movements by a cervical collar may relieve pain. Local injection of anesthetics or corticosteroids, for instance by a pain management specialist, may be of

Peripheral nerve

Nerve root



▲ **Figure 24–2.** Cutaneous innervation. The segmental or radicular (root) distribution is shown on the left side of the body and the peripheral nerve distribution on the right side. Segmental maps show differences depending on how they were constructed (single root stimulation or section; local anesthetic injection into single dorsal root ganglia). (Adapted, with permission, from Aminoff MJ, Greenberg DA, Simon RP. Clinical Neurology, 9th ed. McGraw-Hill Education, 2015.)



▲ Figure 24–2. (Continued)

benefit. Operative treatment may be necessary to prevent further progression if there is a significant neurologic deficit; bowel or bladder symptoms; or if root pain is severe, persistent, and unresponsive to conservative measures.

► When to Refer

- Pain unresponsive to simple measures.
- Patients with neurologic deficits.
- Patients in whom surgical treatment is under consideration.

► When to Admit

- Patients with progressive or significant neurologic deficit.
- Patients with sphincter involvement (from cord compression).
- Patients requiring surgical treatment.

Stino AM et al. Myelopathies due to structural cervical and thoracic disease. *Continuum (Minneapolis Minn)*. 2018;24:567. [PMID: 29613900]

BRACHIAL & LUMBAR PLEXUS LESIONS

1. Brachial Plexus Neuropathy

Brachial plexus neuropathy may be idiopathic, sometimes occurring in relationship to a number of different nonspecific illnesses or factors. In other instances, brachial plexus lesions follow trauma or result from congenital anomalies, neoplastic involvement, or injury by various physical agents. In rare instances, the disorder occurs on a familial basis.

Idiopathic brachial plexus neuropathy (**neuralgic amyotrophy**) characteristically begins with severe pain about the shoulder, followed within a few days by weakness, reflex changes, and sensory disturbances involving especially the C5 and C6 segments but affecting any nerve in the brachial plexus. Symptoms and signs are usually unilateral but may be bilateral. Wasting of affected muscles is sometimes profound. The disorder relates to disturbed function of cervical roots or part of the brachial plexus, but its precise cause is unknown. Recovery occurs over the ensuing months but may be incomplete. Treatment is purely symptomatic, although emerging evidence suggests that microsurgical neurolysis of hourglass-like constrictions on affected nerves identified by magnetic resonance neurography or high-resolution ultrasound improves outcome in patients who have not recovered after several months of conservative management.

2. Cervical Rib Syndrome

Compression of the C8 and T1 roots or the lower trunk of the brachial plexus by a cervical rib or band arising from the seventh cervical vertebra leads to weakness and wasting of intrinsic hand muscles, especially those in the thenar eminence, accompanied by pain and numbness in the medial two fingers and the ulnar border of the hand and forearm. Electromyography, nerve conduction studies, and somatosensory evoked potential studies may help confirm the diagnosis. MRI may be especially helpful in revealing the underlying compressive structure. Plain radiographs or CT scanning sometimes shows the cervical rib or a large transverse process of the seventh cervical vertebra, but normal findings do not exclude the possibility of a cervical band. Treatment of the disorder is by surgical excision of the rib or band.

3. Lumbosacral Plexus Lesions

A lumbosacral plexus lesion may develop in association with diseases such as diabetes, cancer, or bleeding disorders or in relation to injury. It occasionally occurs as an isolated phenomenon similar to idiopathic brachial plexopathy (nondiabetic lumbosacral radiculoplexus neuropathy), and pain and weakness then tend to be more conspicuous than sensory symptoms. The distribution of symptoms and signs depends on the level and pattern of neurologic involvement.

DISORDERS OF NEUROMUSCULAR TRANSMISSION

1. Myasthenia Gravis



ESSENTIALS OF DIAGNOSIS

- ▶ Fluctuating weakness of commonly used voluntary muscles, producing symptoms such as diplopia, ptosis, and difficulty in swallowing.
- ▶ Activity increases weakness of affected muscles.
- ▶ Short-acting anticholinesterases transiently improve the weakness.

► General Considerations

Myasthenia gravis occurs at all ages, *sometimes in association with a thymic tumor or thyrotoxicosis*, as well as in rheumatoid arthritis and lupus erythematosus. It is most common in young women with HLA-DR3; if thymoma is associated, older men are more commonly affected. Onset is usually insidious, but the disorder is sometimes unmasked by a coincidental infection that leads to exacerbation of symptoms. Exacerbations may also occur before the menstrual period and during or shortly after pregnancy. Symptoms are due to a variable degree of block of neuromuscular transmission caused by autoantibodies binding to acetylcholine receptors; these are found in most patients with the disease and have a primary role in reducing the number of functioning acetylcholine receptors. Additionally, cellular immune activity against the receptor is found.

► Clinical Findings

A. Symptoms and Signs

Patients present with ptosis, diplopia, difficulty in chewing or swallowing, respiratory difficulties, limb weakness, or some combination of these problems. Weakness may remain localized to a few muscle groups or may become generalized. The external ocular muscles and certain other cranial muscles, including the masticatory, facial, and pharyngeal muscles, are especially likely to be affected, and the respiratory and limb muscles may also be involved. Symptoms often fluctuate in intensity during the day, and this diurnal variation is superimposed on a tendency to longer-term spontaneous relapses and remissions that may last for weeks. Nevertheless, the disorder follows a slowly progressive course and may have a fatal outcome owing to respiratory complications such as aspiration pneumonia.

Clinical examination confirms the weakness and fatigability of affected muscles. In most cases, the extraocular muscles are involved, and this leads to ocular palsies and ptosis, which are commonly asymmetric. Pupillary responses are normal. The bulbar and limb muscles are often weak, but the pattern of involvement is variable. Sustained activity of affected muscles increases the weakness,

which improves after a brief rest. Sensation is normal, and there are usually no reflex changes.

Life-threatening exacerbations of myasthenia (so-called **myasthenic crisis**) may lead to respiratory weakness requiring immediate admission to the intensive care unit, where respiratory function can be monitored and ventilator support is readily available.

B. Laboratory and Other Studies

Assay of serum for elevated levels of circulating acetylcholine receptor antibodies is useful because it has a sensitivity of 80–90% for the diagnosis of myasthenia gravis. Certain patients without antibodies to acetylcholine receptors have serum antibodies to muscle-specific tyrosine kinase (MuSK), which should therefore be determined; these patients are more likely to have facial, respiratory, and proximal muscle weakness than those with antibodies to acetylcholine receptors. Other antibodies associated with myasthenia gravis include low-density lipoprotein receptor-related protein 4 (LRP4) and agrin, but tests for these antibodies are not widely commercially available.

Electrophysiologic demonstration of a decrementing muscle response to repetitive 2- or 3-Hz stimulation of motor nerves indicates a disturbance of neuromuscular transmission. Such an abnormality may even be detected in clinically strong muscles with certain provocative procedures. Needle electromyography of affected muscles shows a marked variation in configuration and size of individual motor unit potentials, and single-fiber electromyography reveals an increased jitter, or variability, in the time interval between two muscle fiber action potentials from the same motor unit.

C. Imaging

A CT scan of the chest with and without contrast should be obtained to demonstrate a coexisting thymoma.

► Treatment

Anticholinesterase medications provide symptomatic benefit without influencing the course of the disease. Neostigmine, pyridostigmine, or both can be used, the dose being determined on an individual basis. The usual dose of neostigmine is 7.5–30 mg (average, 15 mg) orally taken four times daily; of pyridostigmine, 30–180 mg (average, 60 mg) orally four times daily. Overmedication may temporarily increase weakness. A wide range of medications (eg, aminoglycosides) may exacerbate myasthenia gravis and should be avoided.

Thymectomy should be performed when a thymoma is present. A multicenter randomized trial demonstrated the benefit of thymectomy even in the absence of a radiologically identifiable thymoma, with improved strength, lower immunosuppression requirements, and fewer hospitalizations in the surgically treated group. Thus, *thymectomy should be considered in all patients younger than age 65 unless weakness is restricted to the extraocular muscles*. If the disease is of recent onset and only slowly progressive,

operation is sometimes delayed for a year or so, in the hope that spontaneous remission will occur.

Treatment with corticosteroids is indicated for patients who have responded poorly to anticholinesterase medications. Some patients experience transient exacerbation of weakness and even develop respiratory failure within the first 1–2 weeks if corticosteroids are initiated at high doses (eg, prednisone 1 mg/kg/day). Therefore, in stable patients, corticosteroids are introduced gradually in the outpatient setting. Prednisone can be started at 20 mg orally daily and increased by 10 mg increments weekly to a target of 1 mg/kg/day (maximum daily dose 100 mg). For patients hospitalized with severe myasthenia and treated with IVIG or plasmapheresis, the higher dose can be given initially because the more rapid onset of action of the former two therapies mitigates the initial dip in strength due to corticosteroids. Corticosteroids can be prescribed as alternate-day or daily treatment, with alternate-day therapy potentially mitigating side effects. Once the patient has stabilized at the initial high dose, corticosteroids can gradually be tapered to a relatively low maintenance level (eg, 10 mg prednisone orally daily) as improvement occurs; total withdrawal is difficult, however. Treatment with azathioprine may be effective in allowing a lower dose of corticosteroids. The usual dose is 2–3 mg/kg orally daily after a lower initial dose. Other immunosuppressive agents that are used in myasthenia gravis to reduce the corticosteroid dose include mycophenolate mofetil, rituximab, cyclosporine, methotrexate, and tacrolimus. Eculizumab, a complement inhibitor, is approved by the FDA for acetylcholine receptor antibody positive myasthenia in patients who have disease refractory to at least two alternate immunosuppressive therapies. It is administered intravenously (900 mg weekly for four doses, followed by 1200 mg at week 5, then 1200 mg every 2 weeks). Patients must be vaccinated against meningococcus prior to receiving eculizumab.

In patients with major disability, plasmapheresis or IVIG therapy may be beneficial and have similar efficacy. It is also useful for stabilizing patients before thymectomy and for managing acute crisis.

► When to Refer

All patients should be referred.

► When to Admit

- Patients with acute exacerbation or respiratory involvement.
- Patients requiring plasmapheresis.
- For thymectomy.

Farmakidis C et al. Treatment of myasthenia gravis. *Neurol Clin*. 2018;36:311. [PMID: 29655452]

Muppudi S et al; Regain Study Group. Long-term safety and efficacy of eculizumab in generalized myasthenia gravis. *Muscle Nerve*. 2019;60:14. [PMID: 30767274]

2. Myasthenic Syndrome (Lambert-Eaton Myasthenic Syndrome)



ESSENTIALS OF DIAGNOSIS

- ▶ Variable weakness, typically improving with activity.
- ▶ Dysautonomic symptoms may also be present.
- ▶ A history of malignant disease may be obtained.

► Clinical Findings

Myasthenic syndrome *may be associated with small cell carcinoma*, sometimes developing before the tumor is diagnosed, and occasionally occurs with certain autoimmune diseases. There is defective release of acetylcholine in response to a nerve impulse, caused by P/Q-type voltage-gated calcium channel antibodies, and this leads to weakness, especially of the proximal muscles of the limbs. Unlike myasthenia gravis, however, power steadily *increases* with sustained contraction. The diagnosis can be confirmed electrophysiologically, because the muscle response to stimulation of its motor nerve increases remarkably after exercise or if the nerve is stimulated repetitively at high rates (50 Hz), even in muscles that are not clinically weak.

► Treatment

Treatment with IVIG, plasmapheresis, and immunosuppressive medication therapy (prednisone and azathioprine) may lead to clinical and electrophysiologic improvement, in addition to therapy aimed at tumor when present. Prednisone is usually initiated in a daily dose of 60–80 mg orally and azathioprine in a daily dose of 2 mg/kg orally. Symptomatic therapy includes the use of potassium channel antagonists; of these, amifampridine is a 3,4-diaminopyridine (15–80 mg/day orally in three divided doses) and is approved in the United States and Europe. Guanidine hydrochloride (25–50 mg/kg/day orally in divided doses) is an alternative and is occasionally helpful in seriously disabled patients, but adverse effects of the medication include marrow suppression. The response to treatment with anticholinesterase medications such as pyridostigmine or neostigmine is usually disappointing.

3. Botulism

The toxin of *Clostridium botulinum* prevents the release of acetylcholine at neuromuscular junctions and autonomic synapses. Botulism occurs most commonly following the ingestion of contaminated home-canned food; outbreaks have also occurred among drug abusers due to wound infection after injection of contaminated heroin. The diagnosis should be suggested by the development of sudden, fluctuating, severe weakness with preserved sensation in a previously healthy person. Symptoms begin within 72 hours following ingestion of the toxin and may progress for several days. Typically, there is diplopia, ptosis,

facial weakness, dysphagia, and nasal speech, followed by respiratory difficulty and finally by weakness that appears last in the limbs. Blurring of vision (with unreactive dilated pupils) is characteristic, and there may be dryness of the mouth, constipation (paralytic ileus), and postural hypotension. The tendon reflexes are not affected unless the involved muscles are very weak. If the diagnosis is suspected, the local health authority should be notified and a sample of serum and contaminated food (if available) sent to be assayed for toxin. Support for the diagnosis may be obtained by electrophysiologic studies; with repetitive stimulation of motor nerves at fast rates, the muscle response increases in size progressively.

Patients should be hospitalized in case respiratory assistance becomes necessary. Treatment is with heptavalent antitoxin, in patients without known allergy to horse serum. Potassium channel antagonists may provide symptomatic relief as they do in Lambert-Eaton myasthenic syndrome. Anticholinesterase medications are of no value. Respiratory assistance and other supportive measures should be provided as necessary. Further details are provided in Chapter 33.

4. Disorders Associated with Use of Aminoglycosides

Aminoglycoside antibiotics, eg, gentamicin, may produce a clinical disturbance similar to botulism by preventing the release of acetylcholine from nerve endings, but symptoms subside rapidly as the responsible medication is eliminated from the body. These antibiotics are particularly dangerous in patients with preexisting disturbances of neuromuscular transmission and are therefore best avoided in patients with myasthenia gravis.

MYOPATHIC DISORDERS



ESSENTIALS OF DIAGNOSIS

- ▶ Muscle weakness without sensory loss, often in a characteristic distribution.
- ▶ Serum creatine kinase elevated in most cases.
- ▶ Age at onset, time course, and inheritance pattern may suggest underlying disorder.

► General Considerations

Myopathies can be inherited or acquired. Acquired myopathies often present acutely or subacutely while inherited myopathies are typically insidious in onset. Patients typically complain of weakness affecting proximal muscles, such as difficulty climbing stairs, arising from a chair, or reaching overhead, or of head drop. Sensory symptoms are absent. A detailed family history is required.

Examination shows weakness of proximal muscles. In some cases, there is a more specific pattern of weakness

(eg, quadriceps and finger flexor weakness in inclusion body myositis). Extraocular muscle involvement is rarely seen, except in certain mitochondrial disorders, oculopharyngeal muscular dystrophy, and hyperthyroidism; when present, it should suggest the possibility of a neuromuscular junction disorder. Reflexes are normal or diminished in proportion to the degree of weakness. Sensation is normal.

Initial testing should include serum creatine kinase determination. Consider testing thyroid-stimulating hormone, cortisol, vitamin D, and calcium. Antibodies specific to certain inflammatory myopathies and connective tissue disease can be checked when these conditions are suspected (see Chapter 20). Electromyography will reveal small motor units and early recruitment; it is helpful in confirming the localization of weakness to the muscle and suggesting a suitable site for biopsy, as does MRI. The electromyographic findings may be normal in corticosteroid and mitochondrial myopathies. Muscle biopsy establishes the diagnosis when inflammatory, mitochondrial, metabolic, or certain inherited myopathies are suspected. In cases where the family history or pattern of weakness suggests a

specific genetic disorder, genetic testing can be pursued directly and biopsy may not be needed. Selected common and treatable myopathies are discussed below.

1. Muscular Dystrophies

These inherited myopathic disorders are subdivided by mode of inheritance, age at onset, and clinical features, as shown in Table 24–10. In the **Duchenne** type, pseudohypertrophy of muscles frequently occurs at some stage; intellectual disability is common; and there may be skeletal deformities, muscle contractures, and cardiac involvement. A genetic defect on the short arm of the X chromosome has been identified in Duchenne dystrophy. The affected gene codes for the protein dystrophin, which is markedly reduced or absent from the muscle of patients with the disease. Dystrophin levels are generally normal in the **Becker** variety, but the protein is qualitatively altered. The diagnosis is usually made with genetic testing; muscle biopsy is needed occasionally. Duchenne muscular dystrophy can be recognized early in pregnancy in about 95% of

Table 24–10. Selected muscular dystrophies (listed in order of anatomic location and physiologic underpinning).¹

Disorder	Inheritance	Age at Onset (years)	Distribution	Prognosis	Genetic Association
Duchenne type	X-linked recessive	1–5	Pelvic, then shoulder girdle; later, limb and respiratory muscles.	Rapid progression. Death within about 15 years after onset.	Xp21; Dystrophin (loss of functional expression).
Becker	X-linked recessive	5–25	Pelvic, then shoulder girdle.	Slow progression. May have normal life span.	Xp21; Dystrophin (reduced functional expression).
Limb-girdle (Erb)	Autosomal recessive, dominant, or sporadic	10–30	Pelvic or shoulder girdle initially, with later spread to the other.	Variable severity and rate of progression. Possible severe disability in middle life.	Multiple.
Facioscapulo-humeral	Autosomal dominant	Any age	Face and shoulder girdle initially; later, pelvic girdle and legs.	Slow progression. Minor disability. Usually normal life span.	4q35.2; Double homeobox protein 4. 18p11.32; Structural maintenance of chromosome's flexible hinge domain-containing protein 1.
Emery-Dreifuss	X-linked recessive or autosomal dominant	5–10	Humeroperoneal or scapuloperoneal.	Variable.	Multiple.
Distal	Autosomal dominant or recessive	40–60	Onset distally in extremities; proximal involvement later.	Slow progression.	Multiple.
Oculopharyngeal	Autosomal dominant	Any age	Ptosis, external ophthalmoplegia, and dysphagia.	Slow progression.	14q11.2–q13; Poly (A)-binding protein-2.
Myotonic dystrophy	Autosomal dominant	Any age (usually 20–40)	Face, neck, distal limbs.	Slow progression.	19q13.32; Myotonin-protein kinase. 3q21.3; Cellular nucleic acid-binding protein.

¹Not all possible genetic loci are shown.

women by genetic studies; in late pregnancy, DNA probes can be used on fetal tissue obtained for this purpose by amniocentesis. The genes causing some of the other muscular dystrophies are listed in Table 24–10.

Three antisense oligonucleotides are approved by the FDA for treatment of Duchenne muscular dystrophy. Eteplirsen appears to benefit those patients with a dystrophin mutation amenable to exon 51 skipping; golodirsen and viltolarsen benefit those with a mutation amenable to exon 53 skipping. Patients treated with these antisense oligonucleotides had more functional dystrophin on muscle biopsy than controls and a slower rate of disease progression than matched historical controls. Prednisone (0.75 mg/kg orally daily or 10 mg/kg orally given weekly over 2 days) or deflazacort (0.9 mg/kg orally daily) improves muscle strength and function in boys with Duchenne dystrophy, but side effects need to be monitored. Although both corticosteroid preparations cause similar side effects, weight gain at 1 year is less with deflazacort. Prolonged bed rest must be avoided, as inactivity often leads to worsening of the underlying muscle disease. Physical therapy and orthopedic procedures may help counteract deformities or contractures.

2. Myotonic Dystrophy

Myotonic dystrophy, a slowly progressive, dominantly inherited disorder, usually manifests itself in the third or fourth decade but occasionally appears early in childhood. Two types, with a different genetic basis, have been recognized. Myotonia leads to complaints of muscle stiffness and is evidenced by the marked delay that occurs before affected muscles can relax after a contraction. This can often be demonstrated clinically by delayed relaxation of the hand after sustained grip or by percussion of the belly of a muscle. In addition, there is weakness and wasting of the facial, sternocleidomastoid, and distal limb muscles. Associated clinical features include cataracts, frontal baldness, testicular atrophy, diabetes mellitus, cardiac abnormalities, and intellectual changes. Electromyographic sampling of affected muscles reveals myotonic discharges in addition to changes suggestive of myopathy.

It is difficult to determine whether medication therapy for myotonia is safe or effective. When myotonia is disabling, treatment with a sodium channel blocker—such as phenytoin (100 mg orally three times daily), procainamide (0.5–1 g orally four times daily), or mexiletine (150–200 mg orally three times daily)—may be helpful, but the associated side effects, particularly for antiarrhythmic medications, are often limiting. Neither the weakness nor the course of the disorder is influenced by treatment. Cardiac function should be monitored, and pacemaker placement may be considered if there is evidence of heart block.

3. Myotonia Congenita

Myotonia congenita is commonly inherited as a dominant trait. Generalized myotonia without weakness is usually present from birth, but symptoms may not appear until early childhood. Patients complain of muscle stiffness that is enhanced by cold and inactivity and relieved by exercise.

Muscle hypertrophy, at times pronounced, is also a feature. A recessive form with later onset is associated with slight weakness and atrophy of distal muscles. Treatment with procainamide, tocainide, mexiletine, or phenytoin may help the myotonia, as in myotonic dystrophy.

4. Mitochondrial Myopathies

The mitochondrial myopathies are a clinically diverse group of disorders that on pathologic examination of skeletal muscle with the modified Gomori stain show characteristic “ragged red fibers” containing accumulations of abnormal mitochondria. Patients may present with progressive external ophthalmoplegia or with limb weakness that is exacerbated or induced by activity. Other patients present with central neurologic dysfunction, eg, myoclonic epilepsy (**myoclonic epilepsy, ragged red fiber syndrome, or MERRF**), or the combination of myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (**MELAS**). Migraine is a common symptom. Systemic features include but are not limited to diabetes mellitus, hearing loss, retinopathy, cardiomyopathy, gastric dysmotility, and short stature. The serum creatine kinase is usually normal. Mitochondrial myopathies result from separate abnormalities of mitochondrial DNA. Treatment is symptomatic and palliative, but various experimental approaches are being explored.

5. Acid Maltase Deficiency (Pompe Disease)

This is a glycogen storage disease due to mutations in the gene encoding acid alpha-1,4-glucosidase. Age at presentation ranges from infancy to the late fifties and depends on the degree of residual enzyme activity. The juvenile and adult-onset forms present with slowly progressive proximal weakness that includes respiratory failure. Cardiomyopathy is less common in the adult form. Serum creatine kinase is mildly elevated. Muscle biopsy shows glycogen containing lysosomal vacuoles, but the diagnosis is suggested by detecting reduced acid-1,4-alpha-glucosidase activity on a dried blood spot, and confirmed by genetic testing. Treatment with recombinant alpha-glucosidase (20 mg/kg intravenously every 2 weeks) stabilizes disease progression and results in improvement in respiratory function.

6. Dermatomyositis, Anti-Synthetase Syndromes, Immune-Mediated Necrotizing Myopathies, & Polymyositis

See Chapter 20.

7. Inclusion Body Myositis

This disorder, of unknown cause, begins insidiously, usually after middle age, with progressive proximal weakness of first the lower and then the upper extremities, and affecting facial and pharyngeal muscles. Weakness often begins in the quadriceps femoris in the lower limbs and the forearm flexors in the upper limbs. Distal weakness is usually mild. Serum creatine kinase levels may be normal or increased. The diagnosis is confirmed by muscle biopsy.

Anticytosolic 5'-nucleotidase 1A antibodies are detected in one-third of cases and may be associated with a more severe phenotype. Corticosteroid and immunosuppressive therapy is sometimes offered but is usually ineffective, and IVIG therapy is not recommended.

8. Endocrine Myopathies

Myopathy is observed with hypothyroidism, hyperthyroidism, Cushing syndrome and disease, Addison disease, vitamin D deficiency, and both hyperparathyroidism and hypoparathyroidism (the latter mediated by calcium derangements). In hypothyroidism, there may be associated entrapment neuropathies, and examination may show delayed relaxation of tendon reflexes, muscle enlargement, or myoedema. Hyperthyroidism can cause both distal and proximal weakness and rarely a bulbar myopathy. Serum creatine kinase is normal except in hypothyroid myopathy, which can also be painful. Treatment is of the underlying endocrinopathy.

9. Critical Illness Myopathy

Myopathy may occur in association with critical illness, typically in patients who received neuromuscular blocking agents and corticosteroids. It is frequently discovered when patients unexpectedly require prolonged ventilatory support. There can be an associated sensorimotor polyneuropathy. Serum creatine kinase may be elevated initially but has frequently returned to normal or is below normal by the time the condition is suspected. Treatment is supportive.

10. Toxic Myopathies

Myopathy can occur in patients taking aminocaproic acid, amiodarone, chloroquine, colchicine, corticosteroids, cyclosporine, daptomycin, emetine, fibrates, gemcitabine, nucleoside reverse transcriptase inhibitors, or statin medications. Myopathy also occurs with chronic alcoholism, whereas acute reversible muscle necrosis may occur shortly after acute alcohol, cocaine, or methamphetamine intoxication, and with propofol infusion. Inflammatory myopathy may occur in patients taking penicillamine and can be induced by programmed death-1 inhibitors; myotonia may be induced by clofibrate, and preexisting myotonia may be exacerbated or unmasked by depolarizing muscle relaxants (eg, suxamethonium), beta-blockers (eg, propranolol), fenoterol and, possibly, certain diuretics. Valproic acid can precipitate or worsen myopathy in patients with mitochondrial disorders or carnitine palmitoyltransferase II deficiency.

When to Refer

All patients should be referred to establish the diagnosis and underlying cause.

When to Admit

- For respiratory assistance.
- For rhabdomyolysis.

McDonald CM et al; CINRG Investigators. Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study. Lancet. 2018;391:451. [PMID: 29174484]
Pasnoor M et al. Approach to muscle and neuromuscular junction disorders. Continuum (Minneapolis). 2019;25:1536. [PMID: 31794459]

PERIODIC PARALYSIS SYNDROMES

Periodic paralysis may have a familial (dominant inheritance) basis. The syndromes to be described are *channelopathies* that manifest as abnormal, often potassium-sensitive, muscle-membrane excitability and lead clinically to episodes of flaccid weakness or paralysis, sometimes in association with abnormalities of the plasma potassium level. Strength is initially normal between attacks, but progressive myopathic weakness may develop in up to one-third of patients as they age. **Hypokalemic periodic paralysis** is characterized by attacks that tend to occur on awakening, after exercise, or after a heavy meal and may last for several days. Patients should avoid excessive exertion. A low-carbohydrate and low-salt diet may help prevent attacks. An ongoing attack may be aborted by potassium chloride given orally or by intravenous drip, provided the ECG can be monitored and kidney function is satisfactory. In young Asian men, it is commonly associated with hyperthyroidism; treatment of the endocrine disorder prevents recurrences. A nonselective beta-adrenergic blocker may prevent attacks until the endocrine abnormality has been treated. In **hyperkalemic periodic paralysis**, attacks also tend to occur after exercise but usually last for less than 1 hour. They may be terminated by intravenous calcium gluconate (1–2 g) or by intravenous diuretics (furosemide, 20–40 mg), glucose, or glucose and insulin. **Normokalemic periodic paralysis** is similar clinically to the hyperkalemic variety, but the plasma potassium level remains normal during attacks. Several randomized trials support the use of dichlorphenamide (50–100 mg orally twice daily) for prevention of attacks in both hyperkalemic and hypokalemic periodic paralysis; acetazolamide (250–750 mg orally daily) is also effective. Chlorothiazide may also be used to prevent attacks in hyperkalemic periodic paralysis.

When to Refer

All patients should be referred.

25

Psychiatric Disorders

Kristin S. Raj, MD
Nolan Williams, MD
Charles DeBattista, DMH, MD

The fifth edition of the American Psychiatric Association's *Diagnostic and Statistical Manual (DSM-5)* is the common language that clinicians use for psychiatric conditions. It utilizes specific criteria with which to objectively assess symptoms for use in clinical diagnosis and communication.

COMMON PSYCHIATRIC DISORDERS

ADJUSTMENT DISORDERS



ESSENTIALS OF DIAGNOSIS

- ▶ Anxiety or depression in reaction to an identifiable stressor, though out of proportion to the severity of the stressor.
- ▶ Symptoms are not at the severity of a major depressive episode or with the chronicity of generalized anxiety disorder (GAD).

General Considerations

An individual experiences stress when adaptive capacity is overwhelmed by events. The event may be an insignificant one when objectively considered, and even favorable changes (eg, promotion and transfer) requiring adaptive behavior can produce stress. For everyone, stress is subjectively defined, and the response to stress is a function of each person's personality and physiologic endowment.

Opinion differs about what events are most apt to produce stress reactions. The causes of stress are different at different ages—eg, in young adulthood, the sources of stress are found in the marriage or parent-child relationship, the employment relationship, and the struggle to achieve financial stability; in the middle years, the focus shifts to changing spousal relationships, problems with aging parents, and problems associated with having young adult offspring who themselves are encountering stressful situations; in old age, the principal concerns are apt to be retirement, loss of physical and mental capacity, major personal losses, and thoughts of death.

Clinical Findings

An individual may react to stress by becoming anxious or depressed, by developing a physical symptom, by running away, drinking alcohol, overeating, starting an affair, or in limitless other ways. Common subjective responses are anxiety, sadness, fear, rage, guilt, and shame. Acute and reactivated stress may be manifested by restlessness, irritability, fatigue, increased startle reaction, and a feeling of tension. Inability to concentrate, sleep disturbances (insomnia, bad dreams), and somatic preoccupations sometimes lead to self-medication, most commonly with alcohol or other central nervous system depressants. Emotional and behavioral distressing symptomatology in response to stress is called **adjustment disorder**, with the major symptom specified (eg, “adjustment disorder with depressed mood, anxiety, mixed depression and anxiety, disturbance of conduct, mixed disturbance of emotions and conduct, or unspecified.”). Even with an identifiable stressor, if the patient meets syndromal criteria for another disorder such as major depression, then the convention would be to diagnose a major depression and not an adjustment disorder with depressed mood.

Differential Diagnosis

Adjustment disorders are distinguished from anxiety disorders, mood disorders, bereavement, other stress disorders such as posttraumatic stress disorder (PTSD), and personality disorders exacerbated by stress and from somatic disorders with psychic overlay. Unlike many other psychiatric disorders, such as bipolar disorder or schizophrenia, adjustment disorders are *wholly situational* and usually resolve when the stressor resolves or the individual effectively adapts to the situation. Adjustment disorders may have symptoms that overlap with other disorders, such as anxiety symptoms, but they occur in reaction to an identifiable life stressor such as a difficult work situation or romantic breakup. An adjustment disorder that persists and worsens can potentially evolve into another psychiatric disorder such as major depression or GAD. However, that is not the case for most patients. Patients with adjustment disorders have marked distress after a stressor and significant impairment in social or occupational functioning but

not to the degree experienced by patients with a more severe disorder such as major depressive disorder or PTSD. By definition, an adjustment disorder occurs within 3 months of an identifiable stressor.

► Treatment

A. Behavioral

Stress reduction techniques include immediate symptom reduction (eg, rebreathing in a bag for hyperventilation) or early recognition and removal from a stress source before full-blown symptoms appear. It is often helpful for the patient to keep a daily log of stress precipitators, responses, and alleviators. Relaxation, mindfulness-based stress reduction, and exercise techniques are also helpful in improving the reaction to stressful events.

B. Social

The stress reactions of life crisis problems are a function of psychosocial upheaval. While it is not easy for the patient to make necessary changes (or they would have been made long ago), it is important for the clinician to establish the framework of the problem, since the patient's denial system may obscure the issues. Clarifying the problem in the patient's psychosocial context allows the patient to begin viewing it within the proper frame and facilitates the difficult decisions the patient eventually must make (eg, change of job).

C. Psychological

Prolonged in-depth psychotherapy is seldom necessary in cases of isolated stress response or adjustment disorder. Supportive psychotherapy (see above) with an emphasis on strengthening of existing coping mechanisms is a helpful approach so that time and the patient's own resiliency can restore the previous level of function. In addition, cognitive behavioral therapy has long been established to treat acute stress and facilitate recovery in patients with an adjustment disorder.

D. Pharmacologic

Judicious use of sedatives (eg, lorazepam, 0.5–1 mg two or three times daily orally) for a limited time and as part of an overall treatment plan can provide relief from acute anxiety symptoms. Problems arise when the situation becomes chronic through inappropriate treatment or when the treatment approach supports the development of chronicity. There are occasions where the short-term use of selective serotonin reuptake inhibitors (SSRIs) targeting dysphoria and anxiety may be useful.

► Prognosis

Return to satisfactory function after a short period is part of the clinical picture of this syndrome. Resolution may be delayed if others' responses to the patient's difficulties are thoughtlessly harmful or if the secondary gains outweigh the advantages of recovery. The longer the symptoms persist, the worse the prognosis. There is also evidence that

stress-related disorders are associated with increased risk of autoimmune disease, although this mechanism has yet to be elucidated.

O'Donnell ML et al. Adjustment disorder: current developments and future directions. *Int J Environ Res Public Health*. 2019;16:2537. [PMID: 31315203]

TRAUMA & STRESSOR-RELATED DISORDERS



ESSENTIALS OF DIAGNOSIS

- ▶ Exposure to a traumatic or life-threatening event.
- ▶ Flashbacks, intrusive images, and nightmares, often represent reexperiencing the event.
- ▶ Avoidance symptoms, including numbing, social withdrawal, and avoidance of stimuli associated with the event.
- ▶ Increased vigilance, such as startle reactions and difficulty falling asleep.
- ▶ Symptoms impair functioning.

► General Considerations

Posttraumatic stress disorder (PTSD) has been reclassified from an anxiety disorder to a trauma and stressor-related disorder in the *DSM-5*. PTSD is a syndrome characterized by "reexperiencing" a traumatic event (eg, sexual assault, severe burns, military combat) and decreased responsiveness and avoidance of current events associated with the trauma. Studies using cross-sectional surveys have indicated a higher risk for PTSD amongst frontline workers during the COVID-19 pandemic. The lifetime prevalence of PTSD among adult Americans has been estimated to be 6.8% with a point prevalence of 3.6% and with women having rates twice as high as men. Many individuals with PTSD (20–40%) have experienced other associated problems, including divorce, parenting problems, difficulties with the law, and substance abuse.

► Clinical Findings

The key to establishing the diagnosis of PTSD lies in the *history of exposure to a perceived or actual life-threatening event, serious injury, or sexual violence*. This can include serious medical illnesses, and the prevalence of PTSD is higher in people who have experienced serious illnesses such as cancer. The symptoms of PTSD include intrusive thoughts (eg, flashbacks, nightmares), avoidance (eg, withdrawal), negative thoughts and feelings, and increased reactivity. Patients with PTSD can experience physiologic hyperarousal, including startle reactions, illusions, overgeneralized associations, sleep problems, nightmares, dreams about the precipitating event, impulsivity, difficulties in concentration, and hyperalertness. The symptoms may be precipitated or exacerbated by events that are a reminder of the original traumatic event. Symptoms

frequently arise after a long latency period (eg, child abuse can result in later-onset PTSD). *DSM-5* includes the requirement that the symptoms persist for at least 1 month. In some individuals, the symptoms fade over months or years, and in others they may persist for a lifetime. Those with comorbid chronic pain tend to have heightened PTSD symptoms compared with those without chronic pain.

Differential Diagnosis

In 75% of cases, PTSD occurs with comorbid depression or panic disorder, and there is considerable overlap in the symptom complexes of all three conditions. Acute stress disorder has many of the same symptoms as PTSD, but symptoms persist for only 3 days to a month after the trauma. The other major comorbidity is alcohol and substance abuse. The **Primary Care-PTSD Screen** (<https://www.ptsd.va.gov/professional/assessment/screens/pc-ptsd.asp>) and the **PTSD Checklist** (<https://www.ptsd.va.gov/professional/assessment/adult-sr/ptsd-checklist.asp#obtain>) are two useful screening instruments in primary care clinics or community settings with populations at risk for trauma exposure.

Treatment

A. Psychotherapy

Psychotherapy should be initiated after the diagnosis of PTSD has been established and should be brief (typically 8–12 sessions), once the individual is in a safe environment. Exposure therapy has the strongest evidence in treatment of PTSD among psychotherapies and medications, although those with comorbid depression and refugees may benefit less. Cognitive processing therapy, a form of cognitive behavioral therapy for PTSD, has very strong evidence as well. In these approaches, the individual confronts the traumatic situation and learns to view and experience it with less hyperarousal over time. Posttraumatic stress syndromes respond to interventions that help patients integrate the event in an adaptive way with some sense of mastery in having survived the trauma. Partner relationship problems are a major area of concern, and it is important that the clinician have available a dependable referral source when marriage counseling is indicated.

Treatment of any comorbid substance abuse is an essential part of the recovery process for patients with PTSD. In patients with comorbid substance use disorders, there is evidence for better outcomes when substance abuse treatment is delivered alongside trauma-focused psychotherapy. Support groups and 12-step programs such as Alcoholics Anonymous are often very helpful.

Video telepsychiatry for psychotherapy or medication management is now widely available since the COVID-19 pandemic requires physical distancing. Telepsychiatry allows patients access to resources they may not otherwise have. There is similar efficacy in reduction of PTSD symptoms in women veterans with video teletherapy as with in-person therapy.

B. Pharmacotherapy

SSRIs are helpful in ameliorating depression, panic attacks, sleep disruption, and startle responses in PTSD. Sertraline and paroxetine are approved by the US Food and Drug Administration (FDA) for this purpose, and the SSRIs are the only class of medications approved for the treatment of PTSD. They are, therefore, considered the pharmacotherapy of choice for PTSD. Early treatment of anxious arousal with beta-blockers (eg, propranolol, 80–160 mg orally daily) may lessen the peripheral symptoms of anxiety (eg, tremors, palpitations) but has *not* been shown to help prevent development of PTSD. Similarly, noradrenergic agents such as clonidine (titrated from 0.1 mg orally at bedtime to 0.2 mg three times a day) have been shown to help with the hyperarousal symptoms of PTSD. The alpha-adrenergic blocking agent prazosin (2–10 mg orally at bedtime) has mixed evidence for decreasing nightmares and improving quality of sleep in PTSD. Benzodiazepines, such as clonazepam, are generally thought to be *contraindicated* in the treatment of PTSD. The risks of benzodiazepines, including addiction and disinhibition, are thought to outweigh the anxiolytic and sleep benefits in most patients. Trazodone (25–100 mg orally at bedtime) is commonly prescribed as a non-habit forming hypnotic agent. Second-generation antipsychotics have not demonstrated significant utility in the treatment of PTSD, but agents such as quetiapine 50–300 mg/day may have a limited role in treating agitation and sleep disturbance in PTSD patients. Novel agents such as MDMA (methylenedioxymethamphetamine; also called Ecstasy) have shown early promise in the treatment of PTSD and are in phase 3 trials.

Prognosis

Approximately half of patients with PTSD experience chronic symptoms. Prognosis is best in those with good premorbid psychiatric functioning. Individuals who experience trauma resulting from a natural disaster (eg, earthquake or hurricane) tend to do better than those who experience a traumatic interpersonal encounter (eg, rape or combat). *The sooner therapy is initiated after the trauma, once a diagnosis of PTSD has been established, the better the prognosis.* However, it is *not* beneficial to begin therapy immediately after a trauma since it does not decrease the rate of progression to PTSD. A study published in 2018 comparing sertraline and prolonged exposure therapy for patients with PTSD demonstrated that patients who received their preferred treatment were more likely to be adherent, respond to treatment, and have lower self-reported PTSD, depression, and anxiety symptoms.

Grasser LR et al. Treatments of posttraumatic stress disorder in civilian populations. *Curr Psychiatry Rep.* 2019;21:11. [PMID: 30734097]

Guideline Development Panel for the Treatment of PTSD in Adults, American Psychological Association. Summary of the clinical practice guideline for the treatment of posttraumatic stress disorder (PTSD) in adults. *Am Psychol.* 2019;74:596. [PMID: 31305099]

- Johnson SU et al. PTSD symptoms among health workers and public service providers during the COVID-19 outbreak. *PLoS One.* 2020;15:e0241032. [PMID: 33085716]
- Merz J et al. Comparative efficacy and acceptability of pharmacological, psychotherapeutic, and combination treatments in adults with posttraumatic stress disorder: a network meta-analysis. *JAMA Psychiatry.* 2019;76:904. [PMID: 31188399]
- Raskind MA et al. Trial of prazosin for post-traumatic stress disorder in military veterans. *N Engl J Med.* 2018;378:507. [PMID: 29414272]
- Zoellner LA et al. Doubly randomized preference trial of prolonged exposure versus sertraline for treatment of PTSD. *Am J Psychiatry.* 2019;176:287. [PMID: 30336702]

ANXIETY DISORDERS



- ▶ Persistent excessive anxiety or chronic fear and associated behavioral disturbances.
- ▶ Somatic symptoms referable to the autonomic nervous system or to a specific organ system (eg, dyspnea, palpitations, paresthesias).
- ▶ Not limited to an adjustment disorder.
- ▶ Not a result of physical disorders, other psychiatric conditions (eg, schizophrenia), or drug abuse (eg, cocaine).

► General Considerations

Stress, fear, and anxiety all tend to be interactive. The principal components of anxiety are **psychological** (tension, fears, difficulty in concentration, apprehension) and **somatic** (tachycardia, hyperventilation, shortness of breath, palpitations, tremor, sweating). Sympathomimetic symptoms of anxiety are both a response to a central nervous system state and a reinforcement of further anxiety. Anxiety can become *self-generating*, since the symptoms reinforce the reaction, causing it to spiral. Additionally, avoidance of *triggers* of anxiety leads to reinforcement of the anxiety. The person continues to associate the trigger with anxiety and never relearns through experience that the trigger need not always result in fear, or that anxiety will naturally improve with prolonged exposure to an objectively neutral stressor.

► Clinical Findings

A. Generalized Anxiety Disorder

Anxiety disorders are the most prevalent psychiatric disorders. About 7% of women and 4% of men will meet criteria for GAD over a lifetime. GAD becomes chronic in many patients with over half of patients having the disorder for longer than 2 years. Anxiety disorder in the elderly is twice as common as dementia and four to six times more common than major depression, and it is associated with poorer quality of life and contributes to the onset of disability. The anxiety symptoms of apprehension, worry,

irritability, difficulty in concentrating, insomnia, or somatic complaints are present more days than not for at least 6 months. Manifestations can include cardiac (eg, tachycardia, increased blood pressure), gastrointestinal (eg, increased acidity, nausea, epigastric pain), and neurologic (eg, headache, near-syncope) systems. The focus of the anxiety may be a number of everyday activities.

B. Panic Disorder

Panic attacks are recurrent, unpredictable episodes of intense surges of anxiety accompanied by marked physiologic manifestations. **Agoraphobia**, fear of being in places where escape is difficult, such as open spaces or public places where one cannot easily hide, may be present and may lead the individual to confine his or her life to home. Distressing symptoms and signs such as dyspnea, tachycardia, palpitations, dizziness, paresthesias, choking, smothering feelings, and nausea are associated with feelings of impending doom (alarm response). Although these symptoms may lead to overlap with some of the same bodily complaints found in the somatic symptom disorders, the key to the diagnosis of panic disorder is the psychic pain and suffering the individual expresses. **Panic disorder** is diagnosed when panic attacks are accompanied by a chronic fear of the recurrence of an attack or a maladaptive change in behavior to try to avoid potential triggers of the panic attack. Recurrent **sleep panic attacks** (not nightmares) occur in about 30% of panic disorders. **Anticipatory anxiety** develops in all these patients and further constricts their daily lives. Panic disorder tends to be familial, with onset usually under age 25; it affects 3–5% of the population, and the female-to-male ratio is 2:1. The premenstrual period is one of heightened vulnerability. Patients frequently undergo evaluations for emergent medical conditions (eg, heart attack or hypoglycemia), which are then ruled out before the correct diagnosis is made. Gastrointestinal symptoms (eg, stomach pain, heartburn, diarrhea, constipation, nausea and vomiting) are common, occurring in about one-third of cases. Myocardial infarction, pheochromocytoma, hyperthyroidism, and various recreational drug reactions can mimic panic disorder and should be considered in the differential diagnosis. Patients who have panic disorder can become demoralized, hypochondriacal, agoraphobic, and depressed. These individuals are at increased risk for major depression and suicide. Alcohol abuse (in about 20%) results from self-treatment and is frequently combined with dependence on sedatives. About 25% of panic disorder patients also have obsessive-compulsive disorder (OCD).

C. Phobic Disorders

Simple phobias are fears of a specific object or situation (eg, spiders, height) that are out of proportion to the danger posed, and they tend to be chronic. **Social phobias** are global or specific; in the former, all social situations are poorly tolerated, while the latter group includes **performance anxiety** (eg, fear of public speaking). Agoraphobia is frequently associated with panic attacks, and it often develops in early adult life, making a normal lifestyle difficult. Patients with agoraphobia experience intense fear

about common situations, such as being in open spaces (eg, marketplaces), being in enclosed spaces (eg, theaters), standing in line, or being alone outside of their homes.

Treatment

In all cases, underlying medical disorders must be ruled out (eg, cardiovascular, endocrine, respiratory, and neurologic disorders and substance-related syndromes, both intoxication and withdrawal states).

A. Pharmacologic

1. Generalized anxiety disorder—Antidepressants including the SSRIs and serotonin norepinephrine reuptake

inhibitors (SNRIs) are first-line treatment and safe and effective in the long-term management of GAD. The antidepressants appear to be as effective as the benzodiazepines without the risks of tolerance or dependence. However, benzodiazepines take effect more quickly if not immediately, which can be beneficial in brief acute management (Table 25–1).

Antidepressants are the first-line medications for sustained treatment of GAD; unlike benzodiazepines, they have the advantage of not causing physiologic dependency problems. Antidepressants can themselves be anxiolytic when first started—thus, at the initiation of treatment, patient education and at times concomitant short-term treatment with a benzodiazepine are indicated.

Table 25–1. Commonly used antianxiety and hypnotic agents (listed in alphabetical order within classes).

Medication	Usual Daily Oral Doses	Usual Daily Maximum Doses	Cost for 30 Days of Treatment Based on Maximum Dosage ¹
Benzodiazepines (used for anxiety)			
Alprazolam (Xanax) ²	0.5 mg	4 mg	\$91.80
Chlordiazepoxide (Librium) ³	10–20 mg	100 mg	\$36.75
Clonazepam (Klonopin) ³	1–2 mg	10 mg	\$152.25
Clorazepate (Tranxene) ³	15–30 mg	60 mg	\$560.40
Diazepam (Valium) ³	5–15 mg	30 mg	\$22.26
Lorazepam (Ativan) ²	2–4 mg	4 mg	\$5.46
Oxazepam (Serax) ²	10–30 mg	60 mg	\$126.24
Benzodiazepines (used for sleep)			
Estazolam (Prosom) ²	1 mg	2 mg	\$29.67
Flurazepam (Dalmane) ³	15 mg	30 mg	\$26.31
Quazepam (Doral) ³	7.5 mg	15 mg	\$846.00
Temazepam (Restoril) ²	15 mg	30 mg	\$23.49
Triazolam (Halcion) ⁵	0.125 mg	0.25 mg	\$110.00
Miscellaneous (used for anxiety)			
Buspirone (Buspar) ²	10–30 mg	60 mg	\$217.80
Phenobarbital ³	15–30 mg	90 mg	\$19.00
Miscellaneous (used for sleep)			
Eszopiclone (Lunesta) ⁵	2–3 mg	3 mg	\$349.80
Hydroxyzine (Vistaril) ²	50 mg	100 mg	\$24.53
Ramelteon (Rozerem)	8 mg	8 mg	\$365.70
Suvorexant (Belsomra)	5–10 mg	20 mg	\$460.80
Zaleplon (Sonata) ⁶	5–10 mg	10 mg	\$112.37
Zolpidem (Ambien) ⁵	5–10 mg	10 mg	\$137.10

¹Average wholesale price (AWP) for AB-rated generic when available) for quantity listed. Source: IBM Micromedex Red Book (electronic version) IBM Watson Health, Greenwood, CO, USA. Available at <https://www.micromedexsolutions.com> (cited April 18, 2021). AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions.

²Intermediate physical half-life (10–20 hours).

³Long physical half-life (> 20 hours).

⁴Intravenously for procedures.

⁵Short physical half-life (1–6 hours).

⁶Short physical half-life (about 1 hour).

SSRIs, such as escitalopram and paroxetine, are FDA-approved. The SNRIs venlafaxine and duloxetine are FDA-approved for the treatment of GAD in usual antidepressant doses. Initial daily dosing should start low (37.5–75 mg for venlafaxine and 30 mg for duloxetine) and be titrated upward as needed. Buspirone, sometimes used as an augmenting agent in the treatment of depression and compulsive behaviors, is also effective for generalized anxiety. Buspirone is usually given in a total dose of 30–60 mg/day in divided doses. Higher doses are sometimes associated with side effects of gastrointestinal symptoms and dizziness. Bupropion may be the most anxiogenic antidepressant and does *not* have evidence in treatment of anxiety disorders. There is a 2- to 4-week delay before antidepressants and buspirone take effect, and *patients require education regarding this lag*. Sleep is sometimes negatively affected. Gabapentin (titrated to doses of 900–1800 mg orally daily, with larger doses at night) and pregabalin appear effective and lack the habit-forming potential of the benzodiazepines. Beta-blockers, such as propranolol, may help reduce peripheral somatic symptoms. Alcohol is the most frequently self-administered drug and should be strongly discouraged.

2. Panic disorder—Antidepressants are the first-line pharmacotherapy for panic disorder. Several SSRIs, including fluoxetine, paroxetine, and sertraline, are approved for the treatment of panic disorder. The SNRI venlafaxine is FDA approved for treatment of panic disorder. As with GAD, panic disorder is often a chronic condition; the long-term use of benzodiazepines can result in tolerance or even benzodiazepine dependence. While panic disorder often responds to high-potency benzodiazepines such as clonazepam and alprazolam, the best use of these agents is generally early in the course of treatment concurrently with an antidepressant. Once the antidepressant has begun working after 4 or more weeks, the benzodiazepine may be tapered.

Whether the indications for benzodiazepines are anxiety or insomnia, the medications should be used judiciously. The longer-acting benzodiazepines are used for the treatment of alcohol withdrawal and anxiety symptoms; the intermediate medications are useful as sedatives for insomnia (eg, lorazepam), while short-acting agents (eg, midazolam) are used for medical procedures such as endoscopy. Benzodiazepines may be given orally, and several are available in intramuscular or parenteral formulations. In psychiatric disorders, the benzodiazepines are usually given orally; in controlled medical environments (eg, the intensive care unit [ICU]), where the rapid onset of respiratory depression can be assessed, they often are given intravenously. Lorazepam does not produce active metabolites and has a half-life of 10–20 hours; these characteristics are useful in treating elderly patients or those with liver dysfunction. Ultra-short-acting agents, such as triazolam, have half-lives of 1–3 hours and may lead to rebound withdrawal anxiety. Longer-acting benzodiazepines, such as flurazepam, diazepam, and clonazepam, produce active metabolites, have half-lives of 20–120 hours, and should be avoided in the elderly; however, some clinicians prefer clonazepam because of its long half-life and thus ease of

dosing to once or twice a day. Since people vary widely in their response and since the medications are long lasting, the dosage must be individualized. Once this is established, an adequate and scheduled dose early in the course of symptom development will obviate the need for “pill popping,” which can contribute to dependency problems.

The side effects of all the benzodiazepine antianxiety agents are patient and dose dependent. As the dosage exceeds the levels necessary for sedation, the side effects include disinhibition, ataxia, dysarthria, nystagmus, and delirium. (The patient *should be told not to operate machinery and drive with caution until he or she is well stabilized without side effects*.)

Paradoxical agitation, anxiety, psychosis, confusion, mood lability, and anterograde amnesia have been reported, particularly with the shorter-acting benzodiazepines. These agents produce cumulative clinical effects with repeated dosage (especially if the patient has not had time to metabolize the previous dose), additive effects when given with other classes of sedatives or alcohol, and residual effects after termination of treatment (particularly in the case of medications that undergo slow biotransformation).

Overdosage results in respiratory depression, hypotension, shock syndrome, coma, and death. Flumazenil, a benzodiazepine antagonist, is effective in overdosage. *Overdosage (see Chapter 38) and withdrawal states are medical emergencies.* Serious side effects of chronic excessive dosage are development of tolerance, resulting in increasing dose requirements, and physiologic dependence, resulting in withdrawal symptoms similar in appearance to alcohol and barbiturate withdrawal (withdrawal effects must be distinguished from reemergent anxiety). Abrupt withdrawal of sedative medications may cause serious and even fatal convulsive seizures. Psychosis, delirium, and autonomic dysfunction have also been described. Both duration of action and duration of exposure are major factors related to likelihood of withdrawal.

Common withdrawal symptoms after low to moderate daily use of benzodiazepines are classified as somatic (disturbed sleep, tremor, nausea, muscle aches), psychological (anxiety, poor concentration, irritability, mild depression), or perceptual (poor coordination, mild paranoia, mild confusion). The presentation of symptoms will vary depending on the half-life of the medication. Benzodiazepine interactions with other medications are listed in Table 25–2.

Antidepressants have been used in conjunction with beta-blockers in resistant cases. Propranolol (40–160 mg/day orally) can mute the peripheral symptoms of anxiety without significantly affecting motor and cognitive performance. They block symptoms mediated by sympathetic stimulation (eg, palpitations, tremulousness) but not non-adrenergic symptoms (eg, diarrhea, muscle tension). Contrary to common belief, *they usually do not cause depression as a side effect* and can be used cautiously in patients with depression.

3. Phobic disorders—Social phobias and agoraphobia may be treated with SSRIs, such as paroxetine, sertraline, and fluvoxamine. In addition, phobic disorders often respond to SNRIs such as venlafaxine. Gabapentin is an alternative to antidepressants in the treatment of social phobia in a

Table 25–2. Benzodiazepine interactions with other medications (listed in alphabetical order).

Medication	Effects
Antacids	Decreased absorption of benzodiazepines
Cimetidine	Increased half-life of diazepam and triazolam
Contraceptives	Increased levels of diazepam and triazolam
Digoxin	Alprazolam and diazepam raise digoxin level
Disulfiram	Increased duration of action of sedatives
Isoniazid	Increased plasma diazepam
Levodopa	Inhibition of antiparkinsonism effect
Propoxyphene	Impaired clearance of diazepam
Rifampin	Decreased plasma diazepam
Warfarin	Decreased prothrombin time

dosage of 300–3600 mg/day, depending on response versus sedation. Specific phobias such as performance or test anxiety may respond to moderate doses of beta-blockers, such as propranolol, 20–40 mg 1 hour prior to exposure. Specific phobias tend to respond to behavioral therapies such as systematic desensitization, which is when the patient is gradually exposed to the feared object or situation in a controlled setting.

B. Behavioral

Behavioral approaches are widely used in various anxiety disorders, often in conjunction with medication. Any of the behavioral techniques can be used beneficially in altering the contingencies (precipitating factors or rewards) supporting any anxiety-provoking behavior. Relaxation techniques can sometimes be helpful in reducing anxiety. Desensitization, by exposing the patient to graded doses of a phobic object or situation, is an effective technique and one that the patient can practice outside the therapy session. Emotive imagery, wherein the patient imagines the anxiety-provoking situation while at the same time learning to relax, helps decrease the anxiety when the patient faces the real-life situation. Physiologic symptoms in panic attacks respond well to relaxation training. *Both GAD and panic disorder appear to respond as well to cognitive behavioral therapy as they do to medications.* Exercise, both aerobic and resistance training, has demonstrated effects in reducing anxiety symptoms across many anxiety disorders as well.

C. Psychological

Cognitive behavioral therapy is the first-line psychotherapy in treatment of anxiety disorders. Cognitive behavioral therapy for anxiety disorders includes a cognitive component of examining the thoughts associated with the fear, and a behavioral technique of exposing the individual to the feared object or situation. The combination of medication and cognitive behavioral therapy is more effective than either alone. **Mindfulness meditation** can also be

effective in decreasing symptoms of anxiety. **Group therapy** is the treatment of choice when the anxiety is clearly a function of the patient's difficulties in dealing with social settings. **Acceptance and commitment therapy** have been used with some success in anxiety disorders. It encourages individuals to keep focused on life goals while they "accept" the presence of anxiety in their lives.

D. Social

Peer support groups for panic disorder and agoraphobia have been particularly helpful. Social modification may require measures such as family counseling to aid acceptance of the patient's symptoms and avoid counterproductive behavior in behavioral training. Any help in maintaining the social structure is anxiety-alleviating, and work, school, and social activities should be maintained. School and vocational counseling may be provided by professionals, who often need help from the clinician in defining the patient's limitations.

► Prognosis

Anxiety disorders are usually long-standing and may be difficult to treat. All can be relieved to varying degrees with medications and behavioral techniques. The prognosis is better if the commonly observed anxiety-panic-phobia-depression cycle can be broken with a combination of the therapeutic interventions discussed above.

Bandelow B. Current and novel psychopharmacological drugs for anxiety disorders. *Adv Exp Med Biol.* 2020;1191:347. [PMID: 32002937]

Slee A et al. Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis. *Lancet.* 2019;393:768. [PMID: 30712879]

OBSESSIVE-COMPULSIVE DISORDER & RELATED DISORDERS

ESSENTIALS OF DIAGNOSIS

- ▶ Preoccupations or rituals (repetitive psychologically triggered behaviors) that are distressing to the individual.
- ▶ Symptoms are excessive or persistent beyond potentially developmentally normal periods.

► General Considerations

Obsessive-compulsive disorder (OCD), classified as an anxiety disorder in the *DSM-IV*, now is part of a separate category of Obsessive-Compulsive Disorder and Related Disorders in *DSM-5*. In OCD, the irrational idea or impulse repeatedly and unwantedly intrudes into awareness. **Obsessions** (recurring distressing thoughts, such as fears of exposure to germs) and **compulsions** (repetitive actions such as washing one's hands many times or

cognitions such as counting rituals) are usually recognized by the individual as unwanted or unwarranted and are resisted, but anxiety often is alleviated only by ritualistic performance of the compulsion or by deliberate contemplation of the intruding idea or emotion. Some patients with OCD only experience obsessions, while some experience both obsessions and compulsions. Many patients do not volunteer the symptoms and must be asked about them. There is an overlapping of OCD with some features in other disorders (“**OCD spectrum**”), including tics, trichotillomania (hair pulling), excoriation disorder (skin picking), hoarding, and body dysmorphic disorder. The incidence of OCD in the general population is 2–3% and there is a high comorbidity with major depression: major depression will develop in two-thirds of OCD patients during their lifetime. Male-to-female ratios are similar, with the highest rates occurring in the young, divorced, separated, and unemployed (all high-stress categories). Neurologic abnormalities of fine motor coordination and involuntary movements are common. Under extreme stress, these patients sometimes exhibit paranoid and delusional behaviors, often associated with depression, that can mimic schizophrenia.

► Treatment

A. Pharmacologic

OCD responds to serotonergic antidepressants including SSRIs and clomipramine in about 60% of cases and usually requires a longer time to response than depression (up to 12 weeks). Fluoxetine has been widely used in this disorder but in doses higher than those used in depression (up to 60–80 mg orally daily). The other SSRI medications, such as sertraline, paroxetine, and fluvoxamine, are used with comparable efficacy each with its own side-effect profile. Clomipramine has proved effective in doses equivalent to those used for depression. Plasma levels of clomipramine and its metabolite should be checked 2–3 weeks after a dosing of 50 mg/day has been achieved, with levels being kept under 500 ng/mL to avoid toxicity. There is some evidence that antipsychotics, topiramate, memantine, riluzole, N-acetylcysteine, lamotrigine, ondansetron, and anti-inflammatory medication (minocycline, celecoxib) may be helpful as adjuncts to the SSRIs in treatment-resistant cases. Preliminary studies have suggested a role for ketamine and esketamine in the treatment of OCD. Small randomized trials have suggested up to 50% of patients get some relief of their OCD symptoms within 1 week of a ketamine infusion. Unfortunately, the effects of ketamine on OCD are short-lived, and further studies are required to confirm efficacy and optimal dosing.

B. Behavioral

OCD may respond to a variety of behavioral techniques. One common strategy is **exposure and response prevention**. As in the treatment of simple phobias, exposure and response prevention involves gradually exposing the OCD spectrum patient to situations that the patient fears, such as perceived germs or situations that a hoarder must part with things they are hoarding. By gradually exposing patients to increasingly stressful situations and helping them manage

their anxiety without performing the unwanted behavior, OCD spectrum patients are often able to develop some mastery over the behaviors.

C. Psychological

In addition to behavioral techniques, OCD may respond to psychological therapies including cognitive behavioral therapy in which the patient learns to identify maladaptive cognitions associated with obsessive thoughts and challenge those cognitions. For example, a patient with OCD may fear that if he does not wash his hands 50 times after shaking hands, he or someone close to him might develop a serious disease. These cognitions can be identified and gradually replaced with more rational thoughts. **Exposure and response prevention** is a form of cognitive behavioral therapy used in the treatment of OCD. Patients work through a list of their obsessions and compulsions with their therapist by first exposing themselves to the trigger, then working to prevent the habitual thought or compulsion that accompanies it. There is evidence that both cognitive behavioral therapy and exposure and response prevention and medications combined can be more effective than a single intervention alone.

D. Social

OCD can have devastating effects on the ability of a patient to lead a normal life. Educating both the patient and family about the course of illness and treatment options is extremely useful in setting appropriate expectations. Severe OCD is commonly associated with vocational disability, and the clinician may sometimes need to facilitate a leave of absence from work or encourage vocational rehabilitation to get the patient back to work.

E. Procedures

Transcranial magnetic stimulation also is effective and FDA-approved for OCD. Psychosurgery has a limited place in selected cases of severe unremitting OCD. Experimental work suggests a role for deep brain stimulation in OCD, and it is FDA approved on a humanitarian device exemption basis for refractory OCD patients.

► Prognosis

OCD is usually a chronic disorder with a waxing and waning course. As many as 40% of patients in whom OCD problems develop in childhood will experience remission as adults. However, it is less common for OCD to remit without treatment when it develops during adulthood.

Beaulieu AM et al. The psychopharmacology algorithm project at the Harvard South Shore Program: an algorithm for adults with obsessive-compulsive disorder. Psychiatry Res. 2019; 281:112583. [PMID: 31600606]

Carmi L et al. Efficacy and safety of deep transcranial magnetic stimulation for obsessive-compulsive disorder: a prospective multicenter randomized double-blind placebo-controlled trial. Am J Psychiatry. 2019;176:931. [PMID: 31109199]

Stein DJ et al. Obsessive-compulsive disorder. Nat Rev Dis Primers. 2019;5:52. [PMID: 31371720]

FEEDING & EATING DISORDERS

See Chapter 29.

SOMATIC SYMPTOM DISORDERS (Abnormal Illness Behaviors)



ESSENTIALS OF DIAGNOSIS

- ▶ Prominent physical symptoms may involve one or more organ systems and are associated with distress, impairment, or both.
- ▶ Sometimes able to correlate symptom development with psychosocial stresses.
- ▶ Combination of biogenetic and developmental patterns.

► General Considerations

Any organ system can be affected in somatic symptom disorders. In *DSM-5*, somatic symptom disorders encompass disorders that were listed under somatic disorders in *DSM-IV*, including conversion disorder, hypochondriasis, somatization disorder, and pain disorder secondary to psychological factors. Vulnerability in one or more organ systems and exposure to family members with somatization problems plays a major role in the development of particular symptoms, and the “functional” versus “organic” dichotomy is a hindrance to good treatment. Clinicians should suspect psychiatric disorders in a number of somatic conditions. For example, 45% of patients describing palpitations had lifetime psychiatric diagnoses including generalized anxiety, depression, panic, and somatic symptom disorders. Similarly, 33–44% of patients who undergo coronary angiography for chest pain but have negative results have been found to have panic disorder.

In any patient presenting with a condition judged to be somatic symptom disorder, depression must be considered in the diagnosis.

► Clinical Findings

A. Conversion Disorder (Functional Neurologic Symptom Disorder)

“Conversion” of psychic conflict into physical neurologic symptoms in parts of the body innervated by the sensorimotor system (eg, paralysis, aphonic) is a disorder that commonly occurs concomitantly with panic disorder or depression. The somatic manifestation that takes the place of anxiety is often paralysis, and in some instances the dysfunction may have symbolic meaning (eg, arm paralysis in marked anger so the individual cannot use the arm to strike someone). Nonepileptic seizures can be difficult to differentiate from intoxication states or panic attacks and can occur in patients who also have epileptic seizures. Lack of postictal confusion, closed eyes during the seizure, ictal crying, and a fluctuating course can suggest nonepileptic seizures; some symptoms such as asynchronous movements or

pelvic thrusting can occur in both nonepileptic seizures and frontal lobe seizures (see also Chapter 24). La belle indifférence (an unconcerned affect) is not a significant identifying characteristic, as commonly believed, since individuals even with genuine medical illness may exhibit a high level of denial. It is important to identify physical disorders with unusual presentations (eg, multiple sclerosis, systemic lupus erythematosus).

B. Somatic Symptom Disorder

Somatic symptom disorder is characterized by one or more somatic symptoms that are associated with significant distress or disability. The somatic symptoms are associated with disproportionate and persistent thoughts about the seriousness of the symptoms, a high level of anxiety about health, or excessive time and energy devoted to these symptoms. The patient’s focus on somatic symptoms is usually chronic. Panic, anxiety, and depression are often present, and major depression is an important consideration in the differential diagnosis. There is a significant relationship (20%) to a lifetime history of panic-agoraphobia-depression. It usually occurs before age 30 and is ten times more common in women. Preoccupation with medical and surgical therapy becomes a lifestyle that may exclude other activities. Patients most often first present to primary care physicians and experience reassurance regarding their physical condition as only briefly helpful or dismissive. Patients’ complaints of symptoms should always be first carefully medically evaluated.

C. Factitious Disorders

These disorders, in which symptom production is *intentional*, are not somatic symptom conditions in that symptoms are produced consciously, in contrast to the unconscious process of the other somatic symptom disorders. They are characterized by self-induced or described symptoms or false physical and laboratory findings for the purpose of deceiving clinicians or other health care personnel. The deceptions may involve self-mutilation, fever, hemorrhage, hypoglycemia, seizures, and an almost endless variety of manifestations—often presented in an exaggerated and dramatic fashion (**Munchausen syndrome**). **Factitious disorder imposed on another**, previously termed **Munchausen by proxy**, is diagnosed when someone (often a parent) creates an illness in another person (often a child) for perceived psychological benefit of the first person, such as sympathy or a relationship with clinicians. The duplicity may be either simple or extremely complex and difficult to recognize. The patients are frequently connected in some way with the health professions and there is no apparent external motivation other than achieving the patient role. A poor clinician-patient relationship and “doctor shopping” tend to exacerbate the problem.

► Complications

Sedative and analgesic dependency is the most common iatrogenic complication. Patients may pursue medical or surgical treatments that induce iatrogenic problems. Thus, identifying patients with a potential somatic symptom

disorder and attempting to limit tests, procedures, and medications that may lead to harm are quite important.

► Treatment

A. Medical

Medical support with careful attention to *building a therapeutic clinician-patient relationship is the mainstay of treatment*. It must be accepted that the patient's distress is real. *Every problem not found to have an organic basis is not necessarily a mental disease*. Regular, frequent, short appointments that are not symptom-contingent may be helpful. Medications should *not* be prescribed to replace appointments. One person should be the primary clinician, and consultants should be used mainly for evaluation. An empathic, realistic, optimistic approach must be maintained in the face of the expected ups and downs. Ongoing reevaluation is necessary since somatization can coexist with a concurrent physical illness.

B. Psychological

The primary clinician can use psychological approaches when the patient is ready to make some changes in lifestyle in order to achieve symptomatic relief. This is often best approached with orientation toward pragmatic current changes rather than an exploration of early experiences that the patient frequently fails to relate to current distress. Cognitive behavioral therapy has been shown to be an effective treatment for somatoform disorders by reducing physical symptoms, psychological distress, and disability. Group therapy with other individuals who have similar problems is sometimes of value to improve coping, allow ventilation, and focus on interpersonal adjustment. Hypnosis used early can be helpful in resolving conversion disorders. If the primary clinician has been working with the patient on psychological problems related to the physical illness, the groundwork is often laid for successful psychiatric referral.

For patients who have been identified as having a factitious disorder, early psychiatric consultation is indicated. There are two main treatment strategies for these patients. One consists of a conjoint confrontation of the patient by both the primary clinician and the psychiatrist. The patient's disorder is portrayed as a cry for help, and psychiatric treatment is recommended. The second approach avoids direct confrontation and attempts to provide a face-saving way to relinquish the symptom without overt disclosure of the disorder's origin. Techniques such as biofeedback and self-hypnosis may foster recovery using this strategy.

C. Behavioral

Behavioral therapy is probably best exemplified by **biofeedback** techniques. In biofeedback, the abnormality (eg, increased peristalsis) must be recognized and monitored by the patient and therapist (eg, by an electronic stethoscope to amplify the sounds). This is immediate feedback, and after learning to recognize it, the patient can then learn to identify any change thus produced (eg, a decrease in bowel sounds) and so become a conscious originator of the

feedback instead of a passive recipient. Relief of the symptom operantly conditions the patient to utilize the maneuver that relieves symptoms (eg, relaxation causing a decrease in bowel sounds). With emphasis on this type of learning, the patient is able to identify symptoms early and initiate the countermeasures, thus decreasing the symptomatic problem. Migraine and tension headaches have been particularly responsive to biofeedback methods.

D. Social

Social endeavors include family, work, and other interpersonal activity. Family members should come for some appointments with the patient so they can learn how best to live with the patient. This is particularly important in treatment of somatic and pain disorders. Peer support groups provide a climate for encouraging the patient to accept and live with the problem. Ongoing communication with the employer may be necessary to encourage long-term continued interest in the employee. Employers can become just as discouraged as clinicians in dealing with employees who have chronic problems.

► Prognosis

The prognosis is better if the primary clinician intervenes early before the situation has deteriorated. After the problem has crystallized into chronicity, it is more difficult to effect change.

Liu J et al. The efficacy of cognitive behavioural therapy in somatoform disorders and medically unexplained physical symptoms: a meta-analysis of randomized controlled trials. *J Affect Disord*. 2019;245:98. [PMID: 30368076]

O'Neal MA et al. Treatment for patients with a functional neurological disorder (conversion disorder): an integrated approach. *Am J Psychiatry*. 2018;175:307. [PMID: 29606068]
Scarella TM et al. Illness anxiety disorder: psychopathology, epidemiology, clinical characteristics, and treatment. *Psychosom Med*. 2019;81:398. [PMID: 30920464]

CHRONIC PAIN DISORDERS

► ESSENTIALS OF DIAGNOSIS

- Chronic complaints of pain.
- Symptoms frequently exceed signs.
- Minimal relief with standard treatment.
- History of having seen many clinicians.
- Frequent use of several nonspecific medications.

► General Considerations

A problem in the management of pain is the lack of distinction between acute and chronic pain syndromes. Most clinicians are adept at dealing with acute pain problems but face greater challenges in treating a patient with a chronic pain disorder. Patients with chronic pain can frequently take many medications, stay in bed a great deal, have seen

many clinicians, have lost skills, and experience little joy in either work or play. Relationships suffer (including those with clinicians), and life becomes a constant search for relief. The search results in complex clinician-patient relationships that usually include many medication trials, particularly sedatives, with adverse consequences (eg, irritability, depressed mood) related to long-term use. Treatment failures can provoke angry responses and depression from both the patient and the clinician, and the pain syndrome is exacerbated. When frustration becomes too great, a new clinician is found, and the cycle is repeated. The longer the existence of the pain disorder, the more important become the psychological factors of anxiety and depression. As with all other conditions, it is counterproductive to speculate about whether the pain is "real." *It is real to the patient*, and acceptance of the problem must precede a mutual endeavor to alleviate the disturbance.

Clinical Findings

Components of the chronic pain syndrome consist of anatomic changes, chronic anxiety and depression, anger, and

changed lifestyle. Usually, the anatomic problem is irreversible, since it has already been subjected to many interventions with increasingly unsatisfactory results. An algorithm for assessing chronic pain and differentiating it from other psychiatric conditions is illustrated in Figure 25–1.

Chronic anxiety and depression produce heightened irritability and overreaction to stimuli. A marked decrease in pain threshold is apparent. This pattern develops into a preoccupation with the body and a constant need for reassurance. Patients may have started avoiding usual behaviors when they first developed pain, and then chronic avoidance of usual physical functioning can lead to the development of chronic pain. The pressure on the clinician becomes wearing and often leads to covert rejection of the patient, such as not being available or making referrals to other clinicians.

This is perceived by the patient, who then intensifies the effort to find help, and the typical cycle is repeated. Anxiety and depression are seldom discussed, almost as if there is a tacit agreement not to deal with these issues.

Changes in lifestyle involve some of the pain behaviors. These usually take the form of a *family script* in which the

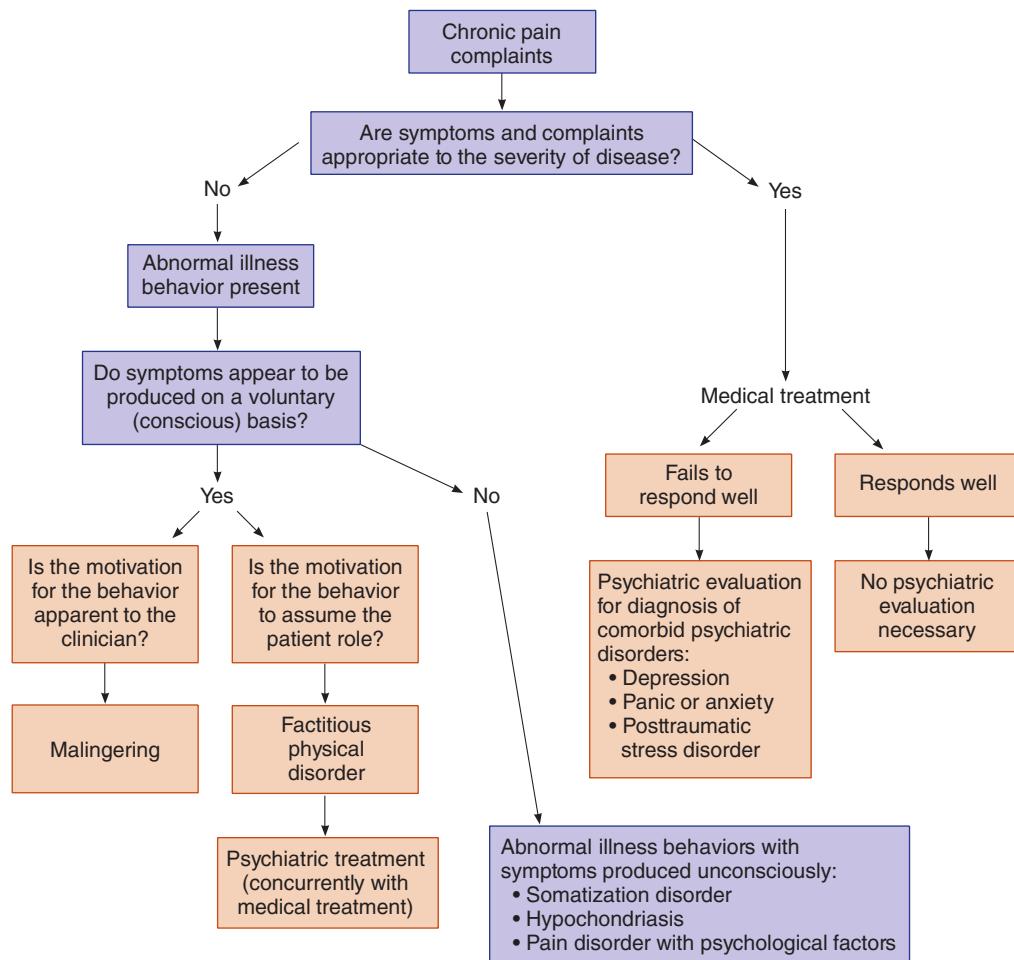


Figure 25–1. Algorithm for assessing psychiatric component of chronic pain. (Adapted and reproduced, with permission, from Eisendrath SJ. Psychiatric aspects of chronic pain. Neurology. 1995;45:S26.)

patient accepts the role of being sick, and this role then becomes the focus of most family interactions and may become important in maintaining the family, so that neither the patient nor the family wants the patient's role to change. Cultural factors frequently play a role in the behavior of the patient and how the significant people around the patient cope with the problem. Some cultures encourage demonstrative behavior, while others value the stoic role.

Another secondary gain that can maintain the patient in the sick role is financial compensation or other benefits. Frequently, such systems are structured so that they reinforce the maintenance of sickness and discourage any attempts to give up the role. Clinicians unwittingly reinforce this role because of the very nature of the practice of medicine, which is to respond to complaints of illness. Helpful suggestions from the clinician are often met with responses like, "Yes, but...." Medications then become the principal approach, and drug dependency problems may develop.

Treatment

A. Behavioral

The cornerstone of a unified approach to chronic pain syndromes is a **comprehensive behavioral program**. This is necessary to identify and eliminate pain reinforcers, to decrease medication use, and to use effectively those positive reinforcers that shift the focus from the pain. It is critical that the patient be made a partner in the effort to manage and function better in the setting of ongoing pain symptoms. *The clinician must shift from the idea of biomedical cure to ongoing care of the patient.* The patient should agree to discuss the pain only with the clinician and not with family members; this tends to stabilize the patient's personal life, since the family is usually tired of the subject. At the beginning of treatment, the patient should be assigned self-help tasks graded up to maximal activity as a means of positive reinforcement. The tasks should not exceed capability. The patient can also be asked to keep a self-rating chart to log accomplishments, so that progress can be measured and remembered. Instruct the patient to record degrees of pain on a self-rating scale in relation to various situations and mental attitudes so that similar circumstances can be avoided or modified.

Avoid positive reinforcers for pain such as marked sympathy and attention to pain. Emphasize a positive response to productive activities, which remove the focus of attention from the pain. Activity is also desensitizing, since the patient learns to tolerate increasing activity levels.

Biofeedback techniques (see Somatic Symptom Disorders, above) and hypnosis have been successful in ameliorating some pain syndromes. Hypnosis tends to be most effective in patients with a high level of denial, who are more responsive to suggestion. Hypnosis can be used to lessen anxiety, alter perception of the length of time that pain is experienced, and encourage relaxation. Mindfulness-based stress reduction programs have been useful in helping individuals develop an enhanced capacity to live a higher quality life with persistent pain.

B. Medical

A single clinician in charge of the comprehensive treatment approach is the highest priority. Consultations as indicated and technical procedures done by others are appropriate, but the care of the patient should remain in the hands of the primary clinician. Referrals should not be allowed to raise the patient's hopes unrealistically or to become a way for the clinician to reject the case. The attitude of the clinician should be one of honesty, interest, and hopefulness—not for a cure but for control of pain and improved function. If the patient manifests opioid addiction, detoxification may be an early treatment goal.

Medical management of chronic pain is addressed in Chapter 5. *The harms of opioids generally outweigh the benefits in chronic pain management.* A fixed schedule lessens the conditioning effects of these medications. SNRIs (eg, venlafaxine, milnacipran, and duloxetine) and TCAs (eg, nortriptyline) in doses up to those used in depression may be helpful, particularly in neuropathic pain syndromes. Both duloxetine and milnacipran are approved for the treatment of fibromyalgia; duloxetine is also indicated in chronic pain conditions. In general, the SNRIs tend to be safer in overdose than the TCAs; suicidality is often an important consideration in treating patients with chronic pain syndromes. Gabapentin and pregabalin, anticonvulsants with possible applications in the treatment of anxiety disorders, have been shown to be useful in neuropathic pain and fibromyalgia.

In addition to medications, a variety of nonpharmacologic strategies may be offered, including physical therapy and acupuncture.

C. Social

Involvement of family members and other significant persons in the patient's life should be an early priority. The best efforts of both patient and therapists can be unwittingly sabotaged by other persons who may feel that they are "helping" the patient. They frequently tend to reinforce the negative aspects of the chronic pain disorder. The patient becomes more dependent and less active, and the pain syndrome becomes an immutable way of life. The more destructive pain behaviors described by many experts in chronic pain disorders are the results of well-meaning but misguided efforts of family members. Ongoing therapy with the family can be helpful in the early identification and elimination of these behavior patterns.

D. Psychological

Cognitive behavioral therapy, acceptance and commitment therapy, and mindfulness-based therapies have evidence in treatment of chronic pain. Therapy can be used in individual or group settings. A major goal, whether of individual or group therapy, is to gain *patient involvement*. A group can be a powerful instrument for achieving this goal, with the development of group loyalties and cooperation. People will frequently make efforts with group encouragement that they would never make alone. Individual therapy should be directed toward strengthening existing coping mechanisms and improving self-esteem. Teaching patients

to challenge expectations induced by chronic pain may lead to improved functioning. As an illustration, many chronic pain patients, making assumptions more derived from acute injuries, *incorrectly believe they will damage themselves by attempting to function*. The rapport between patient and clinician, as in all psychotherapeutic efforts, is a major factor in therapeutic success.

Majeed MH et al. Psychotherapeutic interventions for chronic pain: evidence, rationale, and advantages. *Int J Psychiatry Med.* 2019;54:140. [PMID: 30091372]

Williams ACC et al. Psychological therapies for the management of chronic pain (excluding headache) in adults. *Cochrane Database Syst Rev.* 2020;8:CD007407. [PMID:32794606]

PSYCHOSEXUAL DISORDERS

The stages of sexual activity include **excitement** (arousal), **orgasm**, and **resolution**. The precipitating excitement or arousal is psychologically determined. Arousal response leading to orgasm is a physiologic and psychological phenomenon of vasocongestion, a parasympathetic reaction causing erection in men and labial-clitoral congestion in women. The orgasmic response includes emission in men and clonic contractions of the analogous striated perineal muscles of both men and women. Resolution is a gradual return to normal physiologic status.

While the arousal stimuli—vasocongestive and orgasmic responses—constitute a single response in a well-adjusted person, they can be considered as separate stages that can produce different syndromes responding to different treatment procedures.

Clinical Findings

There are three major groups of sexual disorders.

A. Paraphilias

In these conditions, formerly called “deviations” or “variations,” the excitement stage of sexual activity is associated with sexual objects or orientations different from those usually associated with adult sexual stimulation. The stimulus may be a woman’s shoe, a child, animals, instruments of torture, or incidents of aggression. The pattern of sexual stimulation is usually one that has early psychological roots. When paraphilias are associated with distress, impairment, or risk of harm, they become paraphilic disorders. Some paraphilias or paraphilic disorders include exhibitionism, transvestism, voyeurism, pedophilia, incest, sexual sadism, and sexual masochism.

B. Gender Dysphoria

Gender dysphoria is distress associated with the incongruence between one’s experienced or expressed gender and one’s assigned gender. As a disorder, it is defined by significant distress or impairment; those experiencing this incongruence but without the distress would *not* meet criteria for having gender dysphoria. Screening should be done for conditions related to the oppression and stigmatization that transgender people face, including a high risk of suicide.

C. Sexual Dysfunctions

This category includes a large group of vasocongestive and orgasmic disorders. Often, they involve problems of sexual adaptation, education, and technique that are often initially discussed with, diagnosed by, and treated by the primary care provider.

There are two conditions common in men: erectile dysfunction and ejaculation disturbances.

Erectile dysfunction is inability to achieve or maintain an erection firm enough for satisfactory intercourse; patients sometimes use the term incorrectly to mean premature ejaculation. Decreased nocturnal penile tumescence occurs in some depressed patients. Psychological erectile dysfunction is caused by interpersonal or intrapsychic factors (eg, partner disharmony, depression). Organic factors are discussed in Chapter 23.

Ejaculation disturbances include premature ejaculation, inability to ejaculate, and retrograde ejaculation. (Ejaculation is possible in patients with erectile dysfunction.) Ejaculation is usually connected with orgasm, and ejaculatory control is an acquired behavior that is minimal in adolescence and increases with experience. Pathogenic factors are those that interfere with learning control, most frequently sexual ignorance. Intrapsychic factors (anxiety, guilt, depression) and interpersonal maladaptation (partner problems, unresponsiveness of mate, power struggles) are also common. Organic causes include interference with sympathetic nerve distribution (often due to surgery or radiation) and the effects of pharmacologic agents (eg, SSRIs or sympatholytics).

In women, the most common forms of sexual dysfunction are orgasmic disorder and hypoactive sexual desire disorder.

Orgasmic disorder is a complex condition in which there is a general lack of sexual responsiveness. The woman has difficulty in experiencing erotic sensation and does not have the vasocongestive response. Sexual activity varies from active avoidance of sex to an occasional orgasm.

Orgasmic dysfunction—in which a woman has a vasocongestive response but varying degrees of difficulty in reaching orgasm—is sometimes differentiated from **anorgasmia**. Causes for the dysfunctions include poor sexual techniques, early traumatic sexual experiences, interpersonal disharmony (partner struggles, use of sex as a means of control), and intrapsychic problems (anxiety, fear, guilt). Organic causes include any conditions that might cause pain in intercourse, pelvic pathology, mechanical obstruction, and neurologic deficits.

Hypoactive sexual desire disorder consists of diminished or absent libido in either sex and may be a function of organic or psychological difficulties (eg, anxiety, phobic avoidance). Any chronic illness can reduce desire as can aging. Hormonal disorders, including hypogonadism or use of antiandrogen compounds such as cyproterone acetate, and chronic kidney disease contribute to deterioration in sexual desire. Alcohol, sedatives, opioids, marijuana, and some medications may affect sexual drive and performance. Menopause may lead to diminution of sexual desire in some women, and testosterone therapy is sometimes warranted as treatment.

Treatment

A. Paraphilias

1. Psychological—Paraphilic disorders, particularly those of a more superficial nature (eg, voyeurism) and those of recent onset, are responsive to psychotherapy in some cases. The prognosis is much better if the motivation comes from the individual rather than the legal system; unfortunately, judicial intervention is frequently the only stimulus to treatment because the condition persists and is reinforced until conflict with the law occurs. Therapies frequently focus on barriers to normal arousal response; the expectation is that the variant behavior will decrease as normal behavior increases.

2. Behavioral—In some cases, paraphilic disorders improve with modeling, role-playing, and conditioning procedures.

3. Social—Although they do not produce a change in sexual arousal patterns or gender role, self-help groups have facilitated adjustment to an often hostile society. Attention to the family is particularly important in helping people in such groups to accept their situation and alleviate their guilt about the role they think they had in creating the problem.

4. Pharmacologic—Medroxyprogesterone acetate, a suppressor of libidinal drive, can be used to mute disruptive sexual behavior in men. Onset of action is usually within 3 weeks, and the effects are generally reversible. Fluoxetine or other SSRIs at depression doses may reduce some of the compulsive sexual behaviors including the paraphilic disorders. A focus of study in the treatment of severe paraphilia has been agonists of luteinizing hormone-releasing hormone (LHRH). Case reports and open label studies suggest that LHRH-agonists may play a role in preventing relapse in some patients with paraphilia.

B. Gender Dysphoria

The Standards of Care for the Health of Transsexual, Transgender, and Gender Nonconforming People is a publication of the World Professional Association for Transgender Health (WPATH), with the goal to provide clinical guidance for health professionals to assist transsexual, transgender, and gender nonconforming people with a path to maximize their health, psychological well-being, and self-fulfillment. The standards of care are based on the best available science and expert professional consensus.

1. Psychological—Individuals with gender dysphoria often find benefit from psychotherapy, providing them with a safe place to explore and understand their thoughts and feelings, and to identify their own specific needs and desires and adjust to a changing life.

2. Social—Peer support groups, parent psychoeducation and support, and community empowerment are important social components of treatment.

3. Medical—Some individuals with gender dysphoria choose to pursue surgery or hormone therapy or both. Medical care can also include gynecologic and urologic

care, reproductive options, and voice and communication therapy. Most recommendations prior to surgery include that the individual spends significant time prior living as their desired gender. Rates of suicide fall significantly after surgery but still remain much higher than the general population.

C. Sexual Dysfunction

1. Psychological—The use of psychotherapy by itself is best suited for those cases in which interpersonal difficulties or intrapsychic problems predominate. Anxiety and guilt about parental injunctions against sex may contribute to sexual dysfunction. Even in these cases, however, a combined behavioral-psychological approach usually produces results most quickly.

2. Behavioral—Syndromes resulting from conditioned responses have been treated by conditioning techniques, with excellent results. Masters and Johnson have used behavioral approaches in all of the sexual dysfunctions, with concomitant supportive psychotherapy and with improvement of the communication patterns of the couple.

3. Social—The proximity of other people (eg, a mother-in-law) in a household is frequently an inhibiting factor in sexual relationships. In such cases, some social engineering may alleviate the problem.

4. Medical—Even if the condition is not reversible, identification of the specific cause helps the patient to accept the condition. Partner disharmony, with its exacerbating effects, may thus be avoided. Of all the sexual dysfunctions, erectile dysfunction is the condition most likely to have an organic basis. Sildenafil, tadalafil, and vardenafil are phosphodiesterase type 5 inhibitors that are effective oral agents for the treatment of penile erectile dysfunction (eg, sildenafil 25–100 mg orally 1 hour prior to intercourse). These agents are effective for SSRI-induced erectile dysfunction in men and in some cases for SSRI-associated sexual dysfunction in women. Use of the medications in conjunction with any nitrates can have significant hypotensive effects leading to death in rare cases. Because of their common effect in delaying ejaculation, the SSRIs have been effective in premature ejaculation.

Flibanserin is a 5-HT_{1A}-agonist/5-HT₂-antagonist that is FDA approved for the treatment of female hypoactive sexual desire disorder. Women treated with flibanserin have a marginally higher number of sexual events. The medication interacts with alcohol, causing hypotensive events, so patients need to be educated about this risk. Flibanserin is taken 100 mg orally at bedtime to circumvent the side effects of dizziness, sleepiness, and nausea.

In addition to flibanserin, a second medication was approved by the FDA in 2019 for the treatment of hypoactive sexual desire disorder in premenopausal women. Bremelanotide activates melanocortin receptors, although the mechanism of action in hypoactive sexual desire disorder is unclear. It is self-administered by injection to the thigh or abdomen about 45 minutes before anticipated sexual activity. The subjective improvement to women is

low, however, and both medications carry potentially intolerable side effects, so the use rates of these medications remain low.

Clayton AH et al. Female sexual dysfunction. *Med Clin North Am*. 2019;103:681. [PMID: 31078200]

McMahon CG. Current diagnosis and management of erectile dysfunction. *Med J Aust*. 2019;210:469. [PMID: 31099420]

Nguyen HB et al. Gender-affirming hormone use in transgender individuals: impact on behavioral health and cognition. *Curr Psychiatry Rep*. 2018;20:110. [PMID: 30306351]

PERSONALITY DISORDERS

ESSENTIALS OF DIAGNOSIS

- ▶ Long history dating back to childhood.
- ▶ Recurrent maladaptive behavior.
- ▶ Difficulties with interpersonal relationships or society.
- ▶ Depression with anxiety when maladaptive behavior fails.

► General Considerations

An individual's personality structure, or character, is an integral part of self-image. It reflects genetics, interpersonal influences, and recurring patterns of behavior adopted to cope with the environment. The classification of subtypes of personality disorders depends on the predominant symptoms and their severity. The most severe disorders—those that bring the patient into greatest conflict with society—tend to be antisocial (psychopathic) or borderline.

► Classification & Clinical Findings

See Table 25–3.

► Differential Diagnosis

Patients with personality disorders tend to experience anxiety and depression when pathologic coping mechanisms fail and may first seek treatment when this occurs. Occasionally, the more severe cases may decompensate into psychosis under stress and mimic other psychotic disorders.

► Treatment

A. Social

Social and therapeutic environments such as day hospitals, halfway houses, and self-help communities utilize peer “pressure” to modify the self-destructive behavior. The patient with a personality disorder often has failed to profit from experience, and difficulties with authority can impair the learning experience. The use of peer relationships and the repetition possible in a structured setting of a helpful community enhance the behavioral treatment opportunities and increase learning. When problems are detected early, both the school and the home can serve as foci of intensified social pressure to change the behavior, particularly with the use of behavioral techniques.

B. Behavioral

Dialectical behavioral therapy is a program of individual and group therapy specifically designed for patients with chronic suicidality and borderline personality disorder. It blends mindfulness and a cognitive-behavioral model to address self-awareness, interpersonal functioning, affective lability, and reactions to stress.

Table 25–3. Personality disorders: Classification and clinical findings (listed in alphabetical order).

Personality Disorder	Clinical Findings
Antisocial	Selfish, callous, promiscuous, impulsive, unable to learn from experience, often has legal problems.
Avoidant	Fears rejection, hyperreacts to rejection and failure, with poor social endeavors and low self-esteem.
Borderline	Impulsive; has unstable and intense interpersonal relationships; is suffused with anger, fear, and guilt; lacks self-control and self-fulfillment; has identity problems and affective instability; is suicidal (a serious problem—up to 80% of hospitalized borderline patients make an attempt at some time during treatment, and the incidence of completed suicide is as high as 5%); aggressive behavior, feelings of emptiness, and occasional psychotic decompensation.
Dependent	Passive, overaccepting, unable to make decisions, lacks confidence, with poor self-esteem.
Histrionic (hysterical)	Dependent, immature, seductive, egocentric, vain, emotionally labile.
Narcissistic	Exhibitionist, grandiose, preoccupied with power, lacks interest in others, with excessive demands for attention.
Obsessive compulsive	Perfectionist, egocentric, indecisive, with rigid thought patterns and need for control.
Paranoid	Defensive, oversensitive, secretive, suspicious, hyperalert, with limited emotional response.
Schizoid	Shy, introverted, withdrawn, avoids close relationships.
Schizotypal	Superstitious, socially isolated, suspicious, with limited interpersonal ability, eccentric behaviors, and odd speech.

C. Psychological

Psychological interventions can be conducted in group and individual settings. Group therapy is helpful when specific interpersonal behavior needs to be improved. This mode of treatment also has a place with so-called “acting-out” patients, ie, those who frequently act in an impulsive and inappropriate way. The peer pressure in the group tends to impose restraints on rash behavior. The group also quickly identifies the patient’s types of behavior and helps improve the validity of the patient’s self-assessment, so that the antecedents of the unacceptable behavior can be effectively handled, thus decreasing its frequency. Individual therapy should initially be supportive, ie, helping the patient to restabilize and mobilize coping mechanisms. If the individual has the ability to observe his or her own behavior, a longer-term and more introspective therapy may be warranted. Psychodynamic psychotherapy can also be an effective treatment, with other specific forms of therapy, including transference-focused psychotherapy, mentalization-based therapy, and schema-focused therapy. The therapist must be able to handle countertransference feelings (which are frequently negative), maintain appropriate boundaries in the relationship, and refrain from premature confrontations and interpretations.

D. Pharmacologic

Hospitalization is indicated in the case of serious suicidal or homicidal danger. In most cases, treatment can be accomplished in the day treatment center or self-help community. Pharmacotherapy can be directed to specific symptom clusters, but there is limited evidence for its efficacy in personality disorders. Antidepressants have improved anxiety, depression, and sensitivity to rejection in some patients with borderline personality disorder. SSRIs also have a role in reducing aggressive behavior in impulsive aggressive patients (eg, fluoxetine 20–60 mg orally daily or sertraline 50–200 mg orally daily). Antipsychotics may be helpful in targeting hostility, agitation, and as adjuncts to antidepressant therapy (eg, olanzapine [2.5–10 mg/day orally], risperidone [0.5–2 mg/day orally], or haloperidol [0.5–2 mg/day orally, split into two doses]). In some cases, these medications are required only for several days and can be discontinued after the patient has regained a previously established level of adjustment; they can also provide ongoing support. Anticonvulsants, including carbamazepine, 400–800 mg orally daily in divided doses, lamotrigine, 50–200 mg/day, and valproate 500–2000 mg/day, have been shown to decrease the severity of behavioral dyscontrol in some personality disorder patients. Patients with a schizotypal personality often improve with antipsychotics, while those with avoidant personality may benefit from strategies that reduce anxiety, including the use of SSRIs and benzodiazepines. **Intermittent explosive disorder** is characterized by episodes of unwarranted anger and sometime violence. Antipsychotics and anticonvulsants have been helpful for some patients with intermittent explosive disorder. In addition, there is some initial evidence that the combination of dextromethorphan and quinidine, which is currently approved

for treating pseudobulbar affect, may have a role in the treatment of intermittent explosive disorder. Studies are in progress as of 2021.

► Prognosis

Antisocial and borderline categories generally have a guarded prognosis. Those patients with a history of parental abuse and a family history of mood disorder tend to have the most challenging treatments.

Bayes A et al. Differential diagnosis of bipolar II disorder and borderline personality disorder. *Curr Psychiatry Rep.* 2019;21:125. [PMID: 31749106]

Doering S. Borderline personality disorder in patients with medical illness: a review of assessment, prevalence, and treatment options. *Psychosom Med.* 2019;81:584. [PMID: 31232916]

Faay MDM et al. Efficacy of typical and atypical antipsychotic medication on hostility in patients with psychosis-spectrum disorders: a review and meta-analysis. *Neuropsychopharmacology.* 2018;43:2340. [PMID: 30093698]

SCHIZOPHRENIA SPECTRUM DISORDERS

► ESSENTIALS OF DIAGNOSIS

- Social withdrawal, usually slowly progressive, with decrease in emotional expression or motivation or both.
- Deterioration in personal care with disorganized behaviors or decreased reactivity to the environment or both.
- Disorganized thinking, often inferred from speech that switches topics oddly or is incoherent.
- Auditory hallucinations, often of a derogatory nature.
- Delusions, fixed false beliefs despite conflicting evidence, frequently of a persecutory nature.

► General Considerations

Schizophrenia is manifested by a massive disruption of thinking, mood, and overall behavior as well as poor filtering of stimuli. The cause of schizophrenia is believed to be multifactorial, with genetic, environmental, and neurotransmitter pathophysiologic components. At present, there is *no laboratory method* for confirming the diagnosis of schizophrenia. There may or may not be a history of a major disruption in the individual’s life (failure, loss, physical illness) before gross psychotic deterioration is evident.

Other psychotic disorders on this spectrum are conditions that are similar to schizophrenia in their acute symptoms, but have a less pervasive influence over the long term. The patient usually attains higher levels of functioning. The acute psychotic episodes tend to be less disruptive of the person’s lifestyle, with a fairly quick return to previous levels of functioning.

► Classification

A. Schizophrenia

Schizophrenia is the most common of the psychotic disorders that are all characterized by a loss of contact with reality. The term *psychosis* is broad and most often refers to having one or more of the following: paranoia, auditory hallucinations, and delusions. One percent of the population suffers from schizophrenia. Schizophrenia is a chronic disorder that is characterized by increasing social and vocational disability that begins in late adolescence or early adulthood and tends to continue through life. The average age of onset for men is 18 years and for women is 25 years. Symptoms have been classified into positive and negative categories. **Positive symptoms** include hallucinations, delusions, and disorganized speech; these symptoms appear to be related to increased dopaminergic (D_2) activity in the mesolimbic region, and all patients have at least one or two of these symptoms to meet criteria for diagnosis. There is often a component of paranoia involved. They may also have disorganized behavior. **Negative symptoms** include diminished sociability, restricted affect, and poverty of speech; these symptoms appear to be related to decreased D_2 activity in the mesocortical system. Level of functioning is markedly below that before the onset of symptoms, which must last at least 6 months in some form.

B. Delusional Disorder

Delusional disorders are psychoses in which the predominant symptoms are persistent delusions (ie, beliefs that are false yet fixed despite being shown evidence that they are unfounded) with *minimal* impairment of daily functioning. Intellectual and occupational activities are little affected, whereas social and partner functioning tends to be markedly involved. Hallucinations are not usually present. Common delusional themes include paranoid delusions of persecution, delusions of being related to or loved by a well-known person, and delusions that one's partner is unfaithful.

C. Schizoaffective Disorder

Schizoaffective disorders are those cases that fail to fit comfortably either in the schizophrenia or in the affective categories. They are usually cases with affective symptoms (either a major depressive episode, manic episode, or hypomanic episode) that precede or develop concurrently with psychotic manifestations, and the psychotic symptoms also occur in the absence of any mood symptoms. The psychotic symptoms begin before the mood episode begins and can continue to linger for some time after resolution of the mood episode but do not remain permanently. Because of this, the long-term prognosis is better than for schizophrenia.

D. Schizophreniform Disorders

Schizophreniform disorders are similar in their symptoms to schizophrenic disorders except that the duration of prodromal, acute, and residual symptoms is longer than 1 month but less than 6 months.

E. Brief Psychotic Disorders

Brief psychotic disorders are defined as psychotic symptoms lasting less than 1 month. They are the result of psychological stress. The shorter duration is significant and correlates with a more acute onset and resolution as well as a much better prognosis.

► Clinical Findings

A. Symptoms and Signs

The symptoms and signs of schizophrenia *vary markedly among individuals as well as in the same person at different times*. The patient's appearance may be bizarre, although the usual finding is mildly to moderately unkempt. Motor activity is generally reduced, although extremes ranging from catatonic stupor to frenzied excitement occur. Social behavior is characterized by marked withdrawal coupled with disturbed interpersonal relationships and a reduced ability to experience pleasure. Dependency and a poor self-image are common. Verbal utterances are variable, the language being concrete yet symbolic, with unassociated rambling statements (at times interspersed with mutism) during an acute episode. Neologisms (made-up words or phrases), echolalia (repetition of words spoken by others), and verbigeration (repetition of senseless words or phrases) are occasionally present. Affect is usually flattened, with occasional inappropriateness. *Depression is present in many cases* but may be less apparent during the acute psychotic episode and more obvious during recovery. Depression is sometimes confused with akinetic side effects of antipsychotic medications. It is also related to boredom, which increases symptoms and decreases the response to treatment. Work is generally unavailable and time unfilled, providing opportunities for counterproductive activities such as drug abuse, withdrawal, and increased psychotic symptoms.

Thought content may vary from a paucity of ideas to a rich complex of delusional fantasy with archaic thinking. One frequently notes after a period of conversation that little if any information has been conveyed. Incoming stimuli produce varied responses. In some cases, a simple question may trigger explosive outbursts, whereas at other times there may be no overt response whatsoever (catatonia). When paranoid ideation is present, the patient is often irritable and less cooperative. Delusions (false beliefs) are characteristic of paranoid thinking, and they usually take the form of a preoccupation with the supposedly threatening behavior exhibited by other individuals. This ideation may cause the patient to adopt active countermeasures such as locking doors and windows, taking up weapons, covering the ceiling with aluminum foil to counteract radar waves, and other bizarre efforts. Somatic delusions can revolve around issues of bodily decay or infestation. Perceptual distortions usually include auditory hallucinations—visual hallucinations are more commonly associated with organic mental states—and may include illusions (distortions of reality) such as figures changing in size or lights varying in intensity. Cenesthetic hallucinations (eg, a burning sensation in the brain, feeling blood flowing in blood vessels) occasionally occur. Lack of humor, feelings of

dread, depersonalization (a feeling of being apart from the self), and fears of annihilation may be present. Any of the above symptoms generate higher anxiety levels, with heightened arousal and occasional panic and suicidal ideation, as the individual fails to cope.

The development of the acute episode in schizophrenia frequently is the end product of a gradual decompensation. Frustration and anxiety appear early, followed by depression and alienation, along with progressive ineffectiveness in day-to-day coping. This often leads to feelings of panic and increasing disorganization, with loss of the ability to test and evaluate the reality of perceptions. The stage of so-called **psychotic resolution** includes delusions, autistic preoccupations, and psychotic insight, with acceptance of the decompensated state. The process is frequently complicated by the use of caffeine, alcohol, and other recreational drugs. *Life expectancy of patients with schizophrenia is as much as 20% shorter than that of cohorts in the general population* and is often associated with comorbid conditions such as the metabolic syndrome, which may be induced or exacerbated by the atypical antipsychotic agents.

Polydipsia may produce water intoxication with hyponatremia—characterized by symptoms of confusion, lethargy, psychosis, seizures, and occasionally death—in any psychiatric disorder, but most commonly in schizophrenia. These problems exacerbate the schizophrenic symptoms and can be confused with them. Possible pathogenic factors in polydipsia include a hypothalamic defect, inappropriate antidiuretic hormone (ADH) secretion, anti-psychotic medications (anticholinergic effects, stimulation of hypothalamic thirst center, effect on ADH), smoking (nicotine and syndrome of inappropriate antidiuretic hormone [SIADH]), psychotic thought processes (delusions), and other medications (eg, diuretics, antidepressants, lithium, alcohol) (see Chapter 21).

B. Imaging

A full medical evaluation and CT scan or MRI of the brain should be considered in first episodes of psychosis to rule out organic brain conditions.

Ventricular enlargement and cortical atrophy, as seen on CT scan, have been correlated with chronic course, severe cognitive impairment, and nonresponsiveness to antipsychotic medications. Decreased frontal lobe activity seen on PET scan has been associated with negative symptoms.

► Differential Diagnosis

The diagnosis of schizophrenia is best made over time because repeated observations increase the reliability of the diagnosis. One should *not hesitate to reconsider the diagnosis* of schizophrenia in any person who has received that diagnosis in the past, particularly when the clinical course has been atypical. A number of these patients have been found to actually have bipolar disorder, which has responded well to lithium. Manic episodes can mimic schizophrenia. However, schizophrenia is less likely to be associated with the decreased need for sleep, increase in goal-directed activity, and overconfidence, symptoms that

are typical of mania. However, thought disorder, auditory hallucinations, and delusions are commonly seen in manic psychosis.

Psychotic depressions, brief reactive psychosis, delusional disorder, and any illness with psychotic ideation tend to be confused with schizophrenia, partly because of the regrettable tendency to use the terms interchangeably.

Medical disorders such as thyroid dysfunction, adrenal and pituitary disorders, reactions to toxic materials (eg, mercury, PCBs), and almost all of the organic mental states in the early stages must be ruled out. Postpartum psychosis is discussed under Mood Disorders. Complex partial seizures, especially when psychosensory phenomena are present, are an important differential consideration. Toxic drug states arising from prescription, over-the-counter, herbal and street drugs may mimic all of the psychotic disorders. The chronic use of amphetamines, cocaine, and other stimulants frequently produces a psychosis that is almost identical to the acute paranoid schizophrenic episode. Drug-induced psychoses can have all the positive symptoms of schizophrenia but less commonly have the negative symptoms. The presence of formication (sensation of insects crawling on or under the skin) and stereotypy suggests the possibility of stimulant abuse. Phencyclidine, a common street drug, may cause a reaction that is difficult to distinguish from other psychotic disorders. Cerebellar signs, excessive salivation, dilated pupils, and increased deep tendon reflexes should alert the clinician to the possibility of a toxic psychosis. Industrial chemical toxicity (both organic and metallic), degenerative disorders, and metabolic deficiencies must be considered in the differential diagnosis.

Catatonia, a psychomotor disturbance that may involve decreased motor activity, decreased interaction, or excessive and odd motor activity, is frequently assumed to exist solely as a component of schizophrenic disorders. However, it can actually be the end product of a number of illnesses, including a number of organic conditions as well as other psychiatric disorders such as bipolar disorder. Neoplasms, viral and bacterial encephalopathies, central nervous system hemorrhage, metabolic derangements such as diabetic ketoacidosis, sedative withdrawal, and liver and kidney malfunction have all been implicated. It is particularly important to realize that drug toxicity (eg, overdoses of antipsychotic medications such as fluphenazine or haloperidol) can cause catatonic syndrome, which may be misdiagnosed as a catatonic schizophrenia and inappropriately treated with more antipsychotic medication. Catatonia is also seen in other major psychiatric disorders, including bipolar disorder and major depression.

► Treatment

A. Pharmacologic

Antipsychotic medications are the treatment of choice. The relapse rate can be reduced by 50% with proper maintenance antipsychotic therapy. Long-acting, injectable antipsychotics are used in patients who are not adherent to medication recommendations or who do not respond to oral medication, or patients who choose the ease of not taking a daily pill. Side effects are discussed below.

Table 25–4. Commonly used antipsychotic medications (listed in alphabetical order).

Medication	Usual Daily Oral Dose	Usual Daily Maximum Dose ¹	Cost per Unit	Cost for 30 Days of Treatment Based on Maximum Dosage ²
Aripiprazole (Abilify)	10–15 mg	30 mg	\$36.67/30 mg	\$1100.10
Asenapine (Saphris)	10–20 mg	20 mg	\$24.02/10 mg	\$1441.20
Cariprazine (Vraylar)	1.5–6 mg	6 mg	\$50.71/6 mg	\$1521.30
Chlorpromazine (Thorazine; others)	100–400 mg	1 g	\$18.31/200 mg	\$2746.50
Clozapine (Clozaril)	300–450 mg	900 mg	\$1.12/100 mg	\$302.40
Fluphenazine (Permitil, Prolixin) ³	2–10 mg	60 mg	\$1.15/10 mg	\$207.00
Haloperidol (Haldol)	2–5 mg	60 mg	\$2.76/20 mg	\$248.40
Iloperidone (Fanapt)	12–24 mg	24 mg	\$58.98/12 mg	\$3538.80
Loxapine (Loxitane)	20–60 mg	200 mg	\$2.57/50 mg	\$308.40
Lurasidone (Latuda)	40–80 mg	80 mg	\$53.86/80 mg	\$1615.80
Olanzapine (Zyprexa)	5–10 mg	20 mg	\$0.95/20 mg	\$28.50
Paliperidone (Invega)	6–12 mg	12 mg	\$14.67/6 mg	\$880.20
Perphenazine (Trilafon) ³	16–32 mg	64 mg	\$3.90/16 mg	\$468.00
Quetiapine (Seroquel)	200–400 mg	800 mg	\$1.68/400 mg	\$100.80
Risperidone (Risperdal) ⁴	2–6 mg	10 mg	\$3.60/2 mg	\$540.00
Thiothixene (Navane) ³	5–10 mg	80 mg	\$3.36/10 mg	\$806.40
Trifluoperazine (Stelazine)	5–15 mg	60 mg	\$2.45/10 mg	\$441.00
Ziprasidone (Geodon)	40–160 mg	160 mg	\$9.83/80 mg	\$589.80

¹Can be higher in some cases.

²Average wholesale price (AWP, for AB-rated generic when available) for quantity listed. Source: IBM Micromedex Red Book (electronic version) IBM Watson Health, Greenwood, CO, USA. Available at <https://www.micromedexsolutions.com> (cited April 18, 2021). AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions.

³Indicates piperazine structure.

⁴For risperidone, daily doses above 6 mg increase the risk of extrapyramidal syndrome. Risperidone 6 mg is approximately equivalent to haloperidol 20 mg.

Antipsychotic medications include the “**typical or first-generation**” antipsychotics (haloperidol, chlorpromazine, loxapine, perphenazine, fluphenazine) (dopamine [D₂]-receptor antagonists) and the newer “**atypical or second-generation**” antipsychotics (clozapine, risperidone, olanzapine, quetiapine, aripiprazole, ziprasidone, paliperidone, asenapine, iloperidone, lurasidone, and cariprazine) (Tables 25–4 and 25–5). Generally, increasing milligram potency of the typical antipsychotics is associated with decreasing anticholinergic and adrenergic side effects and increasing extrapyramidal symptoms. *Data suggest similar antipsychotic efficacy for first- and second-generation antipsychotics, but a tendency for the second-generation antipsychotics to be better tolerated with less extrapyramidal side effects leading to enhanced compliance.*

Clozapine, the first “atypical” (novel) antipsychotic medication developed, has dopamine (D₄) receptor-blocking activity as well as central serotonergic, histaminergic, and alpha-noradrenergic receptor-blocking activity. It is effective in the treatment of about 30% of psychoses resistant to other antipsychotic medications, and it may have specific efficacy in decreasing suicidality in patients with schizophrenia. Risperidone is an antipsychotic that blocks some

serotonin receptors (5-HT₂) and D₂ receptors. Risperidone causes fewer extrapyramidal side effects than the typical antipsychotics at doses less than 6 mg. It appears to be as effective as haloperidol and possibly as effective as clozapine in treatment-resistant patients without necessitating weekly white cell counts, as required with clozapine therapy. Risperidone-induced hyperprolactinemia, even on low doses, has been reported, and that effect is thought to be more common with risperidone than with other atypical antipsychotics. Risperidone is available in a long-acting injectable preparation.

Olanzapine is a potent blocker of 5-HT₂ and dopamine D₁, D₂, and D₄ receptors. High doses of olanzapine (10–20 mg daily) appear to be more effective than lower doses. The medication is somewhat more effective than haloperidol in the treatment of negative symptoms, such as withdrawal, psychomotor retardation, and poor interpersonal relationships. It is available in an orally disintegrating form for patients who are unable to tolerate standard oral dosing and in an injectable form for the management of acute agitation associated with schizophrenia and bipolar disorder. Olanzapine is available in a long-term injectable preparation, but this formulation tends to be used less

Table 25–5. Relative potency and side effects of antipsychotic medications (listed in alphabetical order).

Medication	Chlorpromazine: Drug Potency Ratio	Anticholinergic Effects ¹	Extrapyramidal Effect ¹
Aripiprazole	1:20	1	1
Chlorpromazine	1:1	4	1
Clozapine	1:1	4	—
Fluphenazine	1:50	1	4
Haloperidol	1:50	1	4
Iloperidone	1:25	1	1
Loxapine	1:10	2	3
Lurasidone	1:5	1	2
Olanzapine	1:20	1	1
Perphenazine	1:10	2	3
Quetiapine	1:1	1	1
Risperidone	1:50	1	3
Thiothixene	1:20	1	4
Trifluoperazine	1:20	1	4
Ziprasidone	1:1	1	1

¹1, weak effect; 4, strong effect.

commonly than other depot formulations because some patients experience severe sedation and delirium, which occurs in about 0.5–1% of patients.

Quetiapine is an antipsychotic with greater 5-HT₂ relative to D₂ receptor blockade as well as a relatively high affinity for alpha-1- and alpha-2-adrenergic receptors. It appears to be as efficacious as haloperidol in treating positive and negative symptoms of schizophrenia, with fewer extrapyramidal side effects even at high doses.

Ziprasidone has both anti-dopamine receptor and anti-serotonin receptor effects, with good efficacy for both positive and negative symptoms of schizophrenia. Aripiprazole is a partial agonist at the dopamine D₂ and serotonin 5-HT₁ receptors and an antagonist at 5-HT₂ receptors, and it is effective against positive and negative symptoms of schizophrenia. It functions as an antagonist or agonist, depending on the dopaminergic activity at the dopamine receptors. This may help decrease side effects. Aripiprazole is approved as an *augmentation* agent for treatment-resistant depression, even when psychosis is not present, and as a maintenance treatment for bipolar disorder. Aripiprazole is available as an acute injectable preparation as well as a long-term injectable preparation that is given once monthly in patients who are not able to adhere to daily oral dosing. Asenapine, approved for the treatment of schizophrenia and bipolar disorder (mixed or manic state), appears to be particularly helpful in treating negative symptoms of schizophrenia. It is available in a transdermal form, which may reduce some side effects associated with the sublingual form. Paliperidone, the active metabolite of risperidone, is available as a capsule and a monthly injection. Lurasidone is FDA-approved and

has been shown to be effective in treating acute decompensation in patients with chronic schizophrenia. Cariprazine is a partial agonist of the D₂ and D₃ receptor and is approved by the FDA for the treatment of schizophrenia and bipolar disorder. Akathisia, weight gain, and insomnia are among the more commonly reported side effects with cariprazine. Because cariprazine is not a potent D₂-antagonist, it is less likely to increase prolactin levels than most antipsychotics. Lumateperone, another second-generation antipsychotic, appears to have a favorable metabolic profile and appears to act on glutamate as well as D₂ and 5-HT₂ receptors. Unlike other antipsychotics, it does not require dose titration because the starting dose of 42 mg/day is the therapeutic dose.

Beyond antipsychotics, there is early evidence that cannabidiol (CBD), at a dose of 1000 mg/day, added on to existing antipsychotic treatment, may improve psychotic symptoms in schizophrenia. This agent may represent a new class of treatment for psychotic disorders. The prescription version of CBD was FDA-approved for treatment of rare childhood epilepsy. It is not yet widely used in clinical practice for schizophrenia, perhaps due to cost or off-label usage.

1. Clinical indications—The antipsychotics are used to treat all forms of the schizophrenias as well as drug-induced psychoses, psychotic depression, augmentation of unipolar depression, acute mania, and the prevention of mood cycles in bipolar disorder. They are also effective in Tourette syndrome and behavioral dyscontrol in autistic patients. While frequently used to treat agitation in dementia patients, no antipsychotic has been shown to be reliably effective in this population and may *increase the risk of early*

mortality in elderly dementia patients. The improvement rate for treating positive symptoms with antipsychotics is about 80%. Patients whose behavioral symptoms worsen with use of antipsychotic medications may have an undiagnosed organic condition such as anticholinergic toxicity.

Symptoms that are ameliorated by these medications include hyperactivity, hostility, aggression, delusions, hallucinations, irritability, and poor sleep. Individuals with acute psychosis and good premorbid function respond quite well. The most common cause of failure in the treatment of acute psychosis is inadequate dosage, and the most common cause of relapse is noncompliance.

Although first-generation antipsychotics are efficacious in the treatment of positive symptoms of schizophrenia, such as hallucinations and delusions, second-generation antipsychotics are thought to have efficacy in reducing positive symptoms and some efficacy in treating negative symptoms. Antidepressant medications may be used in conjunction with antipsychotics if significant depression is present. Resistant cases may require concomitant use of lithium, carbamazepine, or valproic acid. The addition of a benzodiazepine medication to the antipsychotic regimen may prove helpful in treating the agitated or catatonic psychotic patient who has not responded to antipsychotics alone—lorazepam, 1–2 mg orally, can produce a rapid resolution of catatonic symptoms and may allow maintenance with a lower antipsychotic dose. Electroconvulsive therapy (ECT) has also been effective in treating catatonia and in treating schizophrenia when used in combination with medications.

2. Dosage forms and patterns—The dosage range is quite broad (Table 25–4). For example, risperidone can be effective for some patients with psychotic features at 0.25–1 mg orally at bedtime, whereas up to 6 mg/day may be used in a young patient with acute schizophrenia. In an acutely distressed, psychotic patient one might use haloperidol, 10 mg intramuscularly, which is absorbed rapidly and achieves an initial tenfold plasma level advantage over equal oral doses. Psychomotor agitation, racing thoughts, and general arousal are quickly reduced. The dose can be repeated every 3–4 hours; when the patient is less symptomatic, oral doses can replace parenteral administration in most cases. In the elderly, both atypical (eg, risperidone 0.25 mg–0.5 mg daily or olanzapine 1.25 mg daily) and typical (eg, haloperidol 0.5 mg daily or perphenazine 2 mg daily) antipsychotics, often used effectively in small doses for behavioral control, have been linked to premature death in some cases.

Absorption of oral medications may be increased or decreased by concomitant administration of other medications (eg, antacids tend to decrease the absorption of antidepressants). Previous gastrointestinal surgery may alter pH, motility, and surface areas available for drug absorption. There are racial genetic-based enzyme differences in metabolizing the antipsychotic medications—eg, many people of Asian descent require only about half the usual dosage. Bioavailability is influenced by other factors such as smoking or hepatic microsomal enzyme stimulation with alcohol or barbiturates and enzyme-altering medications such as carbamazepine or methylphenidate. Antipsychotic plasma drug level determinations are not currently of major clinical assistance.

Divided daily doses are not necessary after a maintenance dose has been established, and most patients can then be maintained on a single daily dose, usually taken at bedtime. This is particularly appropriate in a case where the sedative effect of the medication is desired for nighttime sleep, and undesirable sedative effects can be avoided during the day. First-episode patients especially should be tapered off medications after about 6 months of stability and carefully monitored; their rate of relapse is lower than that of multiple-episode patients.

Psychiatric patients—particularly paranoid individuals—often neglect to take their medication. In these cases and in patients who do not respond to oral medication, the enanthate and decanoate (the latter is slightly longer-lasting and has fewer extrapyramidal side effects) forms of fluphenazine or the decanoate form of haloperidol may be given by deep subcutaneous injection or intramuscularly to achieve an effect that will usually last 7–28 days. A patient who cannot be depended on to take oral medication (or who overdoses on minimal provocation) will generally agree to come to the clinician's office for a "shot." The usual dose of the fluphenazine long-acting preparations is 25 mg every 2 weeks. Dosage and frequency of administration vary from about 12.5 mg monthly to 100 mg weekly. Use the smallest effective amount as infrequently as possible. A monthly injection of 25 mg of fluphenazine decanoate is equivalent to about 15–20 mg of oral fluphenazine daily. Risperidone was the first atypical antipsychotic available in a long-acting injectable form (25–50 mg intramuscularly every 2 weeks). Concomitant use of a benzodiazepine (eg, lorazepam, 2 mg orally twice daily) may permit reduction of the required dosage of oral or parenteral antipsychotic medication. Long-acting injectables are now available for risperidone, paliperidone, aripiprazole, and olanzapine.

Intravenous haloperidol, the antipsychotic most commonly used by this route, is often used in critical care units in the management of agitated, delirious patients. Intravenous haloperidol should be given no faster than 1 mg/min to reduce cardiovascular side effects, such as torsades de pointes. Current practice indicates that ECG monitoring should be used whenever haloperidol is being administered intravenously.

Some antipsychotic agents are available for intranasal administration. The intranasal form of loxapine has a more rapid onset of action for the treatment of agitation (about 10 minutes) than either intramuscular or oral antipsychotic agents. Also, intranasal administration tends to be less traumatic to patients than getting an injection. However, intranasal loxapine requires the cooperation of the patient and is more expensive than generic antipsychotic injectable preparations.

There have been investigations for novel compounds involving other therapeutics targets such as the glutamate system as well as the inflammatory cascade.

3. Side effects—For both typical and atypical antipsychotic agents, a range of side effects has been reported. The most common anticholinergic side effects include **dry mouth** (which can lead to ingestion of caloric liquids and weight gain or hyponatremia), **blurred near vision**, **urinary retention** (particularly in elderly men with enlarged

prostates), **delayed gastric emptying**, **esophageal reflux**, **ileus**, **delirium**, and precipitation of **acute glaucoma** in patients with narrow anterior chamber angles. Other autonomic effects include **orthostatic hypotension** and **sexual dysfunction**—problems in achieving erection, ejaculation (including retrograde ejaculation), and orgasm in men (approximately 50% of cases) and women (approximately 30%). Delay in achieving orgasm is often a factor in medication noncompliance. **Electrocardiographic changes** occur frequently, but clinically significant arrhythmias are much less common. Elderly patients and those with preexisting cardiac disease are at greater risk. The most frequently seen electrocardiographic changes include diminution of the T wave amplitude, appearance of prominent U waves, depression of the ST segment, and prolongation of the QT interval (Table 25–6). Ziprasidone can produce QTc prolongation. A pretreatment ECG is indicated for patients at risk for cardiac sequelae (including patients taking other medications that might prolong the QTc interval). In some critical care patients, torsades de pointes has been associated with the use of high-dose intravenous haloperidol (usually greater than 30 mg/24 h).

Associations have been suggested between the atypical antipsychotics and new-onset **diabetes**, **hyperlipidemia**, and **weight gain** (Table 25–6). The FDA has particularly noted the risk of hyperglycemia and new-onset diabetes in this class of medication that is *not* related to weight gain. The risk of diabetes mellitus is increased in patients taking clozapine and olanzapine. Monitoring of weight, fasting blood sugar, and lipids prior to initiation of treatment and at regular intervals thereafter is an important part of medication monitoring. The addition of metformin to olanzapine may improve drug-induced weight gain in patients with drug-naïve, first-episode schizophrenia. A new medication, samidorphan, a mu-opioid antagonist, is being studied in conjunction with olanzapine to reduce the amount of associated weight gain and to further reduce psychotic symptoms. This combination pill has had positive results in randomized controlled trials and is being considered for FDA-approval. Samidorphan is also being investigated for addiction, binge-eating disorder, and

treatment-resistant depression. **Lactation and menstrual irregularities** are common (antipsychotic medications should be avoided, if possible, in breast cancer patients because of potential trophic effects of elevated prolactin levels on the breast). Both antipsychotic and antidepressant medications can **inhibit sperm motility**. **Bone marrow depression** and **cholestatic jaundice** occur rarely; these are hypersensitivity reactions, and they usually appear in the first 2 months of treatment. They subside on discontinuance of the medication. There is cross-sensitivity among all of the phenothiazines, and a medication from a different group should be used when allergic reactions occur.

Clozapine is associated with a 1.6% risk of **agranulocytosis** (higher in persons of Ashkenazi Jewish ancestry), and its use must be strictly monitored with weekly blood counts during the first 6 months of treatment, with monitoring every other week thereafter. The risk of developing agranulocytosis is approximately 2.5 times higher in patients with a polymorphism for *HLADQB1* gene. Thus, this genetic test may be worthwhile to perform before initiating clozapine. Discontinuation of the medication requires weekly monitoring of the white blood cell count for 1 month. Clozapine has been associated with fatal myocarditis and is contraindicated in patients with severe heart disease. In addition, clozapine lowers the seizure threshold and has many side effects, including sedation, severe constipation, hypotension, increased liver biochemical levels, hypersalivation, respiratory arrest, weight gain, and changes in both the ECG and the electroencephalogram. Notably, adynamic ileus is a rare side effect of clozapine that can be fatal, and patients should be closely monitored and treated quickly and preemptively for constipation.

Photosensitivity, retinopathy, and hyperpigmentation are associated with use of fairly high dosages of chlorpromazine. The appearance of particulate melanin deposits in the lens of the eye is related to the total dose given, and patients on long-term medication should have periodic eye examinations. Teratogenicity has not been causally related to these medications, but prudence is indicated particularly in the first trimester of pregnancy. The seizure threshold is

Table 25–6. Adverse factors associated with atypical antipsychotic medications (listed in alphabetical order).

Medication	Weight Gain	Hyperlipidemia	New-Onset Diabetes Mellitus	QTc Prolongation ¹
Aripiprazole	+/-	-	-	++
Asenapine	+/-	+/-	+/-	+++
Clozapine	+++	+++	+++	+/-
Lurasidone	-	-	-	-
Olanzapine	+++	+++	+++	+/-
Paliperidone	+	+/-	+/-	+++
Quetiapine	++	++	++	+++
Risperidone	++	++	++	+
Ziprasidone	+/-	-	-	+++

¹QTc prolongation is a side effect of many medications and suggests a possible risk for arrhythmia. Prescriber's Letter 2011;18(12):271207.

lowered, but it is safe to use these medications in epileptics who take anticonvulsants.

The **neuroleptic malignant syndrome (NMS)** is a catatonia-like state manifested by extrapyramidal signs, blood pressure changes, altered consciousness, and hyperpyrexia; it is an uncommon but serious complication of antipsychotic treatment. Muscle rigidity, involuntary movements, confusion, dysarthria, and dysphagia are accompanied by pallor, cardiovascular instability, fever, pulmonary congestion, and diaphoresis and may result in stupor, coma, and death. The cause may be related to a number of factors, including poor dosage control of antipsychotic medication, affective illness, decreased serum iron, dehydration, and increased sensitivity of dopamine receptor sites. Lithium in combination with an antipsychotic medication may increase vulnerability, which is already increased in patients with an affective disorder. In most cases, the symptoms develop within the first 2 weeks of antipsychotic drug treatment. The syndrome may occur with small doses of the medications. Intramuscular administration is a risk factor. Elevated creatine kinase and leukocytosis with a shift to the left are present early in about half of cases. Treatment includes controlling fever and providing fluid support. Dopamine agonists such as bromocriptine, 2.5–10 mg orally three times a day, and amantadine, 100–200 mg orally twice a day, have also been useful. Dantrolene, 50 mg intravenously as needed, is used to alleviate rigidity (do not exceed 10 mg/kg/day due to hepatotoxicity risk). There is ongoing controversy about the efficacy of these three agents as well as the use of calcium channel blockers and benzodiazepines. ECT has been used effectively in resistant cases. Clozapine has been used with relative safety and fair success as an antipsychotic medication for patients who have had NMS.

Akathisia is the most common (about 20%) extrapyramidal symptom. It usually occurs early in treatment (but may persist after antipsychotics are discontinued) and is frequently mistaken for anxiety or exacerbation of psychosis. It is characterized by a subjective desire to be in constant motion followed by an inability to sit or stand still and consequent pacing. It may induce suicidality or feelings of fright, rage, terror, or sexual torment. Insomnia is often present. It is crucial to educate patients in advance about these potential side effects so that the patients do not misinterpret them as signs of increased illness. In all cases, reevaluate the dosage requirement or the type of antipsychotic medication. One should inquire also about cigarette smoking, which in women has been associated with an increased incidence of akathisia. Antiparkinsonism medications (such as trihexyphenidyl, 2–5 mg orally three times daily) may be helpful, but first-line treatment often includes a benzodiazepine (such as clonazepam, 0.5–1 mg orally three times daily). In resistant cases, symptoms may be alleviated by propranolol, 30–80 mg/day orally, diazepam, 5 mg orally three times daily, or amantadine, 100 mg orally three times daily.

Acute dystonias usually occur early, although a late (**tardive**) occurrence is reported in patients (mostly men after several years of therapy) who previously had early severe dystonic reactions and a mood disorder. Younger

patients are at higher risk for acute dystonias. The most common signs are bizarre muscle spasms of the head, neck, and tongue. Frequently present are torticollis, oculogyric crises, swallowing or chewing difficulties, and masseter spasms. Laryngospasm is particularly dangerous. Back, arm, or leg muscle spasms are occasionally reported. Diphenhydramine, 50 mg intramuscularly, is effective for the acute crisis; one should then give benztropine mesylate, 2 mg orally twice daily, for several weeks, and then discontinue gradually, since few of the extrapyramidal symptoms require long-term use of the antiparkinsonism medications (all of which are about equally efficacious—though trihexyphenidyl tends to be mildly stimulating and benztropine mildly sedating).

Drug-induced parkinsonism is indistinguishable from idiopathic parkinsonism, but it is reversible, occurs later in treatment than the preceding extrapyramidal symptoms, and in some cases appears after antipsychotic withdrawal. The condition includes the typical signs of apathy and reduction of facial and arm movements (akinesia, which can mimic depression), festinating gait, rigidity, loss of postural reflexes, and pill-rolling tremor. Patients with AIDS seem particularly vulnerable to extrapyramidal side effects. High-potency antipsychotics often require antiparkinsonism medications. The antipsychotic dosage should be reduced, and immediate relief can be achieved with antiparkinsonism medications in the same dosages as above. After 4–6 weeks, these antiparkinsonism medications can often be discontinued with no recurrent symptoms. In any of the extrapyramidal symptoms, amantadine, 100–400 mg orally daily, may be used instead of the antiparkinsonism medications. Antipsychotic-induced catatonia is similar to catatonic stupor with rigidity, drooling, urinary incontinence, and cogwheeling. It usually responds slowly to withdrawal of the offending medication and use of antiparkinsonism agents.

Tardive dyskinesia is a syndrome of abnormal involuntary stereotyped movements of the face, mouth, tongue, trunk, and limbs that may occur after months or (usually) years of treatment with antipsychotic agents. The syndrome affects 20–35% of patients who have undergone long-term antipsychotic therapy. Predisposing factors include older age, many years of treatment, cigarette smoking, and diabetes mellitus. Pineal calcification is higher in this condition by a margin of 3:1. There are no clear-cut differences among the antipsychotic medications in the development of tardive dyskinesia. (Although the atypical antipsychotics appear to offer a lower risk of tardive dyskinesia, long-term effects have not been investigated.) However, clozapine is unique in that it has been found to treat antipsychotic-induced tardive dyskinesia. Early manifestations of tardive dyskinesia include fine worm-like movements of the tongue at rest, difficulty in sticking out the tongue, facial tics, increased blink frequency, or jaw movements of recent onset. Later manifestations may include bucco-linguo-masticatory movements, lip smacking, chewing motions, mouth opening and closing, disturbed gag reflex, puffing of the cheeks, disrupted speech, respiratory distress, or choreoathetoid movements of the extremities (the last being more prevalent in younger patients).

The symptoms do not necessarily worsen and in rare cases may lessen even though antipsychotic medications are continued. The dyskinesias do not occur during sleep and can be voluntarily suppressed for short periods. Stress and movements in other parts of the body will often aggravate the condition.

Early signs of dyskinesia must be differentiated from those reversible signs produced by ill-fitting dentures or nonantipsychotic medications such as levodopa, TCAs, antiparkinsonism agents, anticonvulsants, and antihistamines. Other neurologic conditions such as Huntington chorea can be differentiated by history and examination.

The emphasis should be on prevention of side effects. Use the least amount of antipsychotic medication necessary to improve the psychotic symptoms. Detect early manifestations of dyskinesias. When these occur, gradually discontinue antipsychotic medications, if clinically feasible. Weight loss and cachexia sometimes appear on withdrawal of antipsychotics. In an indeterminate number of cases, the dyskinesias will remit. Keep the patient off the medications until reemergent psychotic symptoms dictate their resumption, at which point they are restarted in low doses and gradually increased until there is clinical improvement. If antipsychotic medications are restarted, clozapine and olanzapine appear to offer less risk of recurrence. The use of adjunctive agents such as benzodiazepines or lithium may help directly or indirectly by allowing control of psychotic symptoms with a low dosage of antipsychotics. If the dyskinetic syndrome recurs and it is necessary to continue antipsychotic medications to control psychotic symptoms, informed consent should be obtained. Vesicular monoamine transporter 2 (VMAT2) inhibitors, such as valbenazine and deutetetrabenazine, amantadine, vitamin B₆, and vitamin E, and propranolol all have had some usefulness in treating the dyskinetic side effects. The VMAT2 inhibitors are now considered the treatment of choice for tardive dyskinesia and are the only medications FDA approved its treatment. However, as of 2021, they are expensive and not covered by many insurance plans.

B. Social

Environmental considerations are most important in the individual with a chronic illness, who usually has a history of repeated hospitalizations, a continued low level of functioning, and symptoms that never completely remit. Family rejection and work failure are common. In these cases, board and care homes staffed by personnel experienced in caring for psychiatric patients are most important. There is frequently an inverse relationship between stability of the living situation and the amounts of required antipsychotic medications, since the most salutary environment is one that reduces stimuli. Nonresidential self-help groups such as Recovery, Inc., should be utilized whenever possible. They provide a setting for sharing, learning, and mutual support and are frequently the only social involvement with which this type of patient is comfortable. Vocational rehabilitation and work agencies (eg, Goodwill Industries, Inc.) provide assessment, training, and job opportunities at a level commensurate with the person's clinical condition.

C. Psychological

The need for psychotherapy varies markedly depending on the patient's current status and history. In a person with a single psychotic episode and a previously good level of adjustment, supportive psychotherapy may help the patient reintegrate the experience, gain some insight into antecedent problems, and become a more self-observant individual who can recognize early signs of stress. Research suggests that cognitive behavioral therapy—in conjunction with medication management—has efficacy in the treatment of symptoms of schizophrenia. Cognitive behavioral therapy for psychosis involves helping the individual challenge psychotic thinking and alters response to hallucinations. Similarly, a form of psychotherapy called acceptance and commitment therapy has shown value in helping prevent hospitalizations in schizophrenia. Cognitive remediation therapy is another approach to treatment that may help patients with schizophrenia become better able to focus their disorganized thinking. Family therapy may also help alleviate the patient's stress and to assist relatives in coping with the patient.

D. Behavioral

Hospitalization is sometimes necessary, particularly when the patient's behavior shows gross disorganization. The presence of competent family members or social support lessens the need for hospitalization, and each case should be judged individually. The major considerations are to prevent self-inflicted harm or harm to others and to provide for the patient's basic needs.

Behavioral techniques (see above) are most frequently used in therapeutic settings such as day treatment centers, but they can also be incorporated into family situations or any therapeutic setting. Many behavioral techniques (eg, positive reinforcement—whether it be a word of praise or an approving nod—after some positive behavior) can be a powerful instrument for helping a person learn behaviors that will facilitate social acceptance. Music from portable digital players or smartphones with earphones is one of many ways to divert the patient's attention from auditory hallucinations.

► Prognosis

For most patients with any psychosis, the prognosis is good for alleviation of positive symptoms such as hallucinations or delusions treated with medication. Negative symptoms such as diminished affect and sociability are much more difficult to treat but appear mildly responsive to atypical antipsychotics. Cognitive deficits, such as the executive dysfunction that is common to schizophrenia, also do not appear as responsive to antipsychotics as do positive symptoms. Unfortunately, both negative symptoms and cognitive deficits appear to contribute more to long-term disability than do positive symptoms. Unavailability of structured work situations and lack of family therapy or access to other social support are two other reasons why the prognosis is so guarded in such a large percentage of patients.

- Artukoglu BB et al. Pharmacologic treatment of tardive dyskinesia: a meta-analysis and systematic review. *J Clin Psychiatry*. 2020;81:19r12798. [PMID: 32459404]
- Goff DC et al. Citalopram in first episode schizophrenia: the DECIFER trial. *Schizophr Res*. 2019;208:331. [PMID: 30709746]
- Huhn M et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet*. 2019;394:939. [PMID: 31303314]
- Keepers GA et al. The American Psychiatric Association practice guideline for the treatment of patients with schizophrenia. *Am J Psychiatry*. 2020;177:868. [PMID: 32867516]
- McGuire P et al. Cannabidiol (CBD) as an adjunctive therapy in schizophrenia: a multicenter randomized controlled trial. *Am J Psychiatry*. 2018;175:225. [PMID: 29241357]

depression in some heavily impacted communities in Europe and Asia. US national surveys show a three-fold increase in the prevalence of depressive symptoms, with risk factors including lower income, less than \$5000 in savings, and exposure to stressors. Depression may be the final expression of (1) genetic factors (neurotransmitter dysfunction), (2) developmental problems (personality problems, childhood events), or (3) psychosocial stresses (divorce, unemployment). It frequently presents in the form of somatic complaints with negative medical work-ups. *Although sadness and grief are normal responses to loss, depression is not.*

Mania is often combined with depression and may occur alone, together with depression in a mixed episode, or in cyclic fashion with depression.

► Clinical Findings

In general, there are four major types of depression, with similar symptoms in each group.

A. Adjustment Disorder with Depressed Mood

Depressed mood may occur in reaction to some identifiable stressor or adverse life situation, usually loss of a person by death (grief reaction), divorce, etc; financial reversal (crisis); or loss of an established role, such as being needed. Anger is frequently associated with the loss, and this in turn often produces a feeling of guilt. Adjustment disorder by definition *occurs within 3 months of the stressor and causes significant impairment in social or occupational functioning*. The symptoms range from mild sadness, anxiety, irritability, worry, and lack of concentration, discouragement, and somatic complaints to the more severe symptoms of frank depression. *When the full criteria for major depressive disorder are present, however, then that diagnosis should be made and treatment instituted even when there is a known stressor.* The presence of a stressor is not the determining diagnostic driver; it is the resultant syndromal complex. One should not neglect treatment for major depression simply because it may appear to be an understandable reaction to a particular stress or difficulty.

B. Depressive Disorders

The subclassifications include major depressive disorder and dysthymia.

1. Major depressive disorder—A major depressive disorder consists of a syndrome of mood, physical and cognitive symptoms that occurs at any time of life. Many consider a physiologic or metabolic aberration to be causative. Complaints vary widely but most frequently include a loss of interest and pleasure (**anhedonia**), withdrawal from activities, and feelings of guilt. Also included are inability to concentrate, some cognitive dysfunction, anxiety, chronic fatigue, feelings of worthlessness, somatic complaints (unexplained somatic complaints frequently indicate depression), loss of sexual drive, and thoughts of death. Unemployment has been associated with increase in depression risk. Diurnal variation with improvement as the day progresses is common. Vegetative signs that frequently

MOOD DISORDERS (Depression & Mania)

► ESSENTIALS OF DIAGNOSIS

Present in most depressions

- Mood varies from mild sadness to intense despondency and feelings of guilt, worthlessness, and hopelessness.
- Difficulty in thinking, including inability to concentrate, ruminations, and lack of decisiveness.
- Loss of interest, with diminished involvement in work and recreation.
- Somatic complaints such as disrupted, lessened, or excessive sleep; loss of energy; change in appetite; decreased sexual drive.

Present in some severe depressions

- Psychomotor retardation or agitation.
- Delusions of a somatic or persecutory nature.
- Withdrawal from activities.
- Physical symptoms of major severity, eg, anorexia, insomnia, reduced sexual drive, weight loss, and various somatic complaints.
- Suicidal ideation.

Possible symptoms in mania

- Mood ranging from euphoria to irritability.
- Sleep disruption.
- Hyperactivity.
- Racing thoughts.
- Grandiosity or extreme overconfidence.
- Variable psychotic symptoms.

► General Considerations

Depression is extremely common, with up to 30% of primary care patients having depressive symptoms. The COVID-19 pandemic has undoubtedly increased the risk of depression. One meta-analysis of studies of community-based prevalence of depression found a seven-fold increase in

occur are insomnia, anorexia with weight loss, and constipation. Occasionally, severe agitation and psychotic ideation are present. **Psychotic major depression** occurs up to 14% of all patients with major depression and 25% of patients who are hospitalized with depression. Psychotic symptoms (delusions, paranoia) are more common in depressed persons who are older than 50 years. Paranoid symptoms may range from general suspiciousness to ideas of reference with delusions. The somatic delusions frequently revolve around feelings of impending annihilation or somatic concerns (eg, that the body is rotting away with cancer). Hallucinations are less common than unusual beliefs and tend not to occur independent of delusions.

In addition to psychotic major depression, other subcategories include **major depression with atypical features** that is characterized by hypersomnia, overeating, lethargy, and mood reactivity in which the mood brightens in response to positive events or news. **Melancholic major depression** is characterized by a lack of mood reactivity seen in atypical depression, the presence of a prominent anhedonia, and more severe vegetative symptoms. **Major depression with a seasonal onset (seasonal affective disorder)** is a dysfunction of circadian rhythms that occurs more commonly in the fall and winter months and is believed to be due to decreased exposure to full-spectrum light. Common symptoms include carbohydrate craving, lethargy, hyperphagia, and hypersomnia. **Major depression with peripartum onset** occurs during pregnancy or starts up to 4 weeks after delivery.

Half of depressions associated with the peripartum period start during pregnancy. Most women (up to 80%) experience some mild letdown of mood in the postpartum period. For some of these (10–15%), the symptoms are more severe and similar to those usually seen in serious depression, with an increased emphasis on concerns related to the baby (obsessive thoughts about harming it or inability to care for it). When psychotic symptoms occur, there is frequently associated sleep deprivation, volatility of behavior, and manic-like symptoms. Postpartum psychosis is much less common (less than 2%), often occurs within the first 2 weeks, and requires early and aggressive management. Biologic vulnerability with hormonal changes and psychosocial stressors all play a role. The chances of a second episode are about 25% and may be reduced with prophylactic treatment.

2. Persistent depressive disorder (dysthymia)—Dysthymia is a chronic depressive disturbance. Sadness, loss of interest, and withdrawal from activities over a period of 2 or more years with a relatively persistent course are necessary for this diagnosis. Generally, the symptoms are milder but longer-lasting than those in a major depressive episode.

3. Premenstrual dysphoric disorder—Depressive symptoms occur during the late luteal phase (last 2 weeks) of the menstrual cycle. (See also Chapter 18.)

C. Bipolar Disorder

Bipolar disorder consists of episodic mood shifts into mania, major depression, hypomania, and mixed mood states. The ability of bipolar disorder to mimic aspects of

many other coincident major mental health disorders and a high comorbidity with substance abuse can make the initial diagnosis of bipolar disorder difficult. **Bipolar I** is diagnosed when an individual has manic episodes. For individuals who experience hypomanic episodes without frank mania, the diagnosis is **bipolar II**.

1. Mania—A manic episode is a mood state characterized by elation with hyperactivity, overinvolvement in life activities, increased irritability, flight of ideas, easy distractibility, and little need for sleep. The overenthusiastic quality of the mood and the expansive behavior initially attract others, but the irritability, mood lability with swings into depression, aggressive behavior, and grandiosity usually lead to marked interpersonal difficulties. Activities may occur that are later regretted, eg, excessive spending, resignation from a job, a hasty marriage, sexual acting out, and exhibitionistic behavior, with alienation of friends and family. Atypical manic episodes can include gross delusions, paranoid ideation of severe proportions, and auditory hallucinations usually related to some grandiose perception. The episodes begin abruptly (sometimes precipitated by life stresses) and may last from several days to months. Generally, the manic episodes are of shorter duration than the depressive episodes. *In almost all cases, the manic episode is part of a broader bipolar disorder.* Patients with four or more discrete episodes of a mood disturbance in 1 year have “**rapid cycling**.” Substance abuse, particularly cocaine, can mimic rapid cycling.

2. Cyclothymic disorder—This is a chronic mood disturbance with episodes of subsyndromal depression and hypomania. The symptoms must have at least a 2-year duration and are milder than those that occur in depressive or manic episodes. Occasionally, the symptoms will escalate into a full-blown manic or depressive episode, in which case reclassification as bipolar I or II would be warranted.

D. Mood Disorders Secondary to Illness and Medications

Any illness, severe or mild, can cause significant depression. Conditions such as rheumatoid arthritis, multiple sclerosis, stroke, and chronic heart disease are particularly likely to be associated with depression, as are other chronic illnesses. Depression is common in cancer, as well, with a particularly high degree of comorbidity in pancreatic cancer. Hormonal variations clearly play a role in some depressions. Varying degrees of depression occur at various times in schizophrenic disorders, central nervous system disease, and organic mental states. Alcohol dependency frequently coexists with serious depression.

The classic model of **drug-induced depression** occurred with the use of reserpine, both in clinical settings and as a pharmacologic probe in research settings. Corticosteroids are commonly associated with mood changes such as depression and hypomania or psychosis. Antihypertensive medications such as methyldopa, guanethidine, and clonidine have been associated with the development of depressive syndromes, as have digitalis and antiparkinsonism medications (eg, levodopa). Retinoids have been associated with depression, and interferon is strongly associated

with depressed mood and fatigue as a side effect; consultation with a psychiatrist prior to prescribing these agents is indicated in cases where there is a history of depression. Overall, the literature has *not* shown an association between beta-blocker use and depression. Infrequently, disulfiram and anticholinesterase medications may be associated with symptoms of depression. Stimulant use results in a depressive syndrome when the drug is withdrawn. Alcohol, sedatives, and opioids are depressants and, paradoxically, are often used in self-treatment of depression.

Differential Diagnosis

Since depression may be a part of any illness—either reactively or as a secondary symptom—careful attention must be given to personal life adjustment problems and the role of medications (eg, reserpine, corticosteroids, levodopa). Schizophrenia, partial complex seizures, organic brain syndromes, panic disorders, and anxiety disorders must be differentiated. Thyroid dysfunction and other endocrinopathies should be ruled out. Malignancies, including central and gastrointestinal tumors are sometimes associated with depressive symptoms and may antecede the diagnosis of tumor. Strokes, particularly dominant hemisphere lesions, can occasionally present with a syndrome that looks like major depression. Medication-induced depressive symptoms are also quite common.

Complications

The most important complication is **suicide**, which often includes some elements of aggression. Suicide rates in the general population vary from 9 per 100,000 in Spain to 15 per 100,000 in the United States to 31 per 100,000 in Russia. In individuals hospitalized for depression, the lifetime risk rises to 4–6%. In patients with bipolar I disorder, the risk is higher. Men over the age of 50 are more likely to *complete* a suicide because of their tendency to attempt suicide with more violent means, particularly guns. On the other hand, women make more *attempts* but are less likely to complete a suicide. The suicide rate in the younger population, aged 15–35, continues to rise. Patients with cancer, respiratory illnesses, AIDS, and those being maintained on hemodialysis have higher suicide rates. Alcohol use is a significant factor in many suicide attempts.

There are several groups of people who make suicide attempts. One group includes those individuals with acute situational problems. These individuals may be acutely distressed by a recent breakup in a relationship or another type of disappointment. This group also includes those who may not be diagnosed as having depression, but who are overwhelmed by a stressful situation often with an aspect of public humiliation (eg, victims of cyber-bullying). A suicide attempt in such cases may be an impulsive or aggressive act not associated with significant depression.

Another high-risk group includes individuals with severe depression. Severe depression may be due to conditions such as medical illness (eg, people with AIDS have a suicide rate over 20 times that of the general population) or comorbid psychiatric disorders (eg, panic disorders). Anxiety, panic, and fear are major findings in suicidal behavior.

A patient may seem to make a dramatic improvement, but the lifting of depression may be due to the patient's decision to commit suicide. Another high-risk group are individuals with psychotic illness who tend not to verbalize their concerns and are often successful in their suicide attempt, although they make up only a small percentage of the total.

Suicide is 10 times more prevalent in patients with schizophrenia than in the general population, and jumping from bridges is a more common means of attempted suicide by patients with schizophrenia than by others. In one study of 100 people who jumped from bridges, 47% had schizophrenia.

The immediate goal of psychiatric evaluation is to assess the current suicidal risk and the need for hospitalization versus outpatient management. *A useful question is to ask the person how many hours per day he or she thinks about suicide.* If it is more than 1 hour, the individual is at high risk. Further assessing the risk by inquiring about *intent, plans, means, and suicide-inhibiting factors* (eg, strong ties to children or the church) is essential. Alcohol, hopelessness, delusional thoughts, and complete or nearly complete loss of interest in life or ability to experience pleasure are all positively correlated with suicide attempts. Other risk factors are previous attempts, a family history of suicide, medical or psychiatric illness (eg, anxiety, depression, psychosis), male sex, older age, contemplation of violent methods, a humiliating social stressor, and drug use (including long-term sedative or alcohol use), which contributes to impulsiveness or mood swings. Successful treatment of the patient at risk for suicide cannot be achieved if the patient continues to abuse drugs. An attempt is less likely to be suicidal, for example, if small amounts of poison or medication were ingested or scratching of wrists was superficial, if the act was performed near others or with early notification of others, or if the attempt was arranged so that early detection would be anticipated.

The patient's current mood status is best evaluated by direct evaluation of plans and concerns about the future, personal reactions to the attempt, and thoughts about the reactions of others. Measurement of mood is often facilitated by using a standardized instrument such as the **Hamilton** or **Montgomery-Asberg** clinician-administered rating scales or the self-administered **Quick Inventory of Depressive Symptomatology (QIDS-SR 16)**. Scales allow for initial assessment as well as ongoing treatment tracking. Suicide risk can be specifically assessed using an instrument such as the **Columbia-Suicide Severity Risk Scale**, https://cssrs.columbia.edu/wp-content/uploads/C-SSRS_Pediatric-SLC_11.14.16.pdf. The patient's immediate resources should also be assessed—people who can be significantly involved (most important), family support, job situation, financial resources, etc.

If hospitalization is not indicated after a suicide attempt, the clinician must formulate and institute a treatment plan or make an adequate referral. (The National Suicide Prevention Lifeline, 1-800-273-8255, may be of assistance.) Medication should be dispensed in small amounts to at-risk patients. Although TCAs and SSRIs are associated with an equal incidence of suicide attempts, the risk of a

completed suicide is much higher with TCA overdose. Guns and medications should be removed from the patient's household. Driving should be cautioned against until the patient improves. The problem is often worsened by the long-term complications of the suicide attempt, eg, brain damage due to hypoxia, peripheral neuropathies caused by staying for long periods in one position causing nerve compressions, and medical or surgical problems such as esophageal strictures and tendon dysfunctions.

► Treatment of Depression

A. Medical

Milder forms of depression usually do not require medication therapy and can be managed by psychotherapy and the passage of time. In severe cases—particularly when vegetative signs are significant and symptoms have persisted for more than a few weeks—antidepressant medication therapy is often effective. Medication therapy is also suggested by a family history of major depression in first-degree relatives or a past history of prior episodes.

The antidepressant medications may be classified into four groups: (1) the newer antidepressants, including the SSRIs, SNRIs, and bupropion, vilazodone, vortioxetine, and mirtazapine, (2) the TCAs and clinically similar medications, (3) the MAO inhibitors (Table 25–7), and (4) stimulants. ECT and repetitive transcranial magnetic stimulation are procedural treatments for depression. These modalities are described in greater detail below.

Hospitalization is necessary if suicide is a major consideration or if complex treatment modalities are required.

Medication selection is influenced by the history of previous response or lack thereof if that information is available. There is mixed and inconclusive evidence about the utility and cost-effectiveness of genetic testing to choose an antidepressant treatment strategy. A positive family history of response to a particular medication may suggest that the patient will respond similarly. If no background information is available, a medication such as sertraline, 25 mg orally daily and increasing gradually up to 200 mg depending on response and side effects, or venlafaxine at 37.5 mg/day and titrated gradually as indicated to a maximum dose of 225 mg/day can be selected and a *full trial* instituted. The medication trial should be monitored for worsening mood or suicidal ideation with patient assessments every 1–2 weeks until week 6. The STAR*D trial suggests that if there is no response to the first medication, the best alternatives are to *switch to a second agent* that may be from the same or different class of antidepressant; another option if there is partial response is to try *augmenting the first agent* with bupropion (150–450 mg/day), lithium (eg, 300–900 mg/day orally), thyroid medication (eg, liothyronine, 25–50 mcg/day orally), or a second-generation antipsychotic (eg, aripiprazole [5–15 mg/day]). The Agency for Health Care Policy and Research has produced clinical practice guidelines that outline one algorithm of treatment decisions (Figure 25–2).

Cognitive issues such as concentration and memory problems are common to depression; the evidence shows that these issues sometimes persist even after depression

has remitted, with a higher risk in those individuals who have had more depressive episodes.

Psychotic depression should be treated with a combination of an antipsychotic and an antidepressant such as an SSRI at their usual doses. Mifepristone may have specific and early activity against psychotic depression. ECT is generally regarded as the single most effective treatment for psychotic depression, with remission rates between 60% and 90%.

Major depression with atypical features or seasonal onset can be treated with bupropion or an SSRI with good results. MAO inhibitors appear more effective than TCAs, and a MAO inhibitor may be used if more benign antidepressant strategies prove unsuccessful.

Melancholic depression may respond to ECT, TCAs, and SNRIs, which are preferable to SSRIs. However, SSRIs are often used in the treatment of melancholic depression and are effective in many cases.

Caution: Depressed patients often have suicidal thoughts, and the amount of medication dispensed should be appropriately controlled particularly if prescribing a MAO inhibitor, TCA, and to a lesser extent, venlafaxine. At the same time, *adults with untreated depression are at higher risk for suicide than those who are treated sufficiently to reduce symptoms*. It has been thought that in children and adolescent populations, antidepressants may be associated with some slightly increased risk of suicidality. One meta-analysis indicates that suicidality persists even after symptoms of depression are treated, suggesting other causes such as increased impulsivity among younger patients. After age 25, antidepressants may have neutral or possibly protective effects until age 65 years or older. The older TCAs have a narrow therapeutic index. One advantage of the newer medications is their wider margin of safety. Nonetheless, even with newer agents, because of the possibility of suicidality early in antidepressant treatment, close follow-up is indicated. In all cases of pharmacologic management of depressed states, caution is indicated until the risk of suicide is considered minimal.

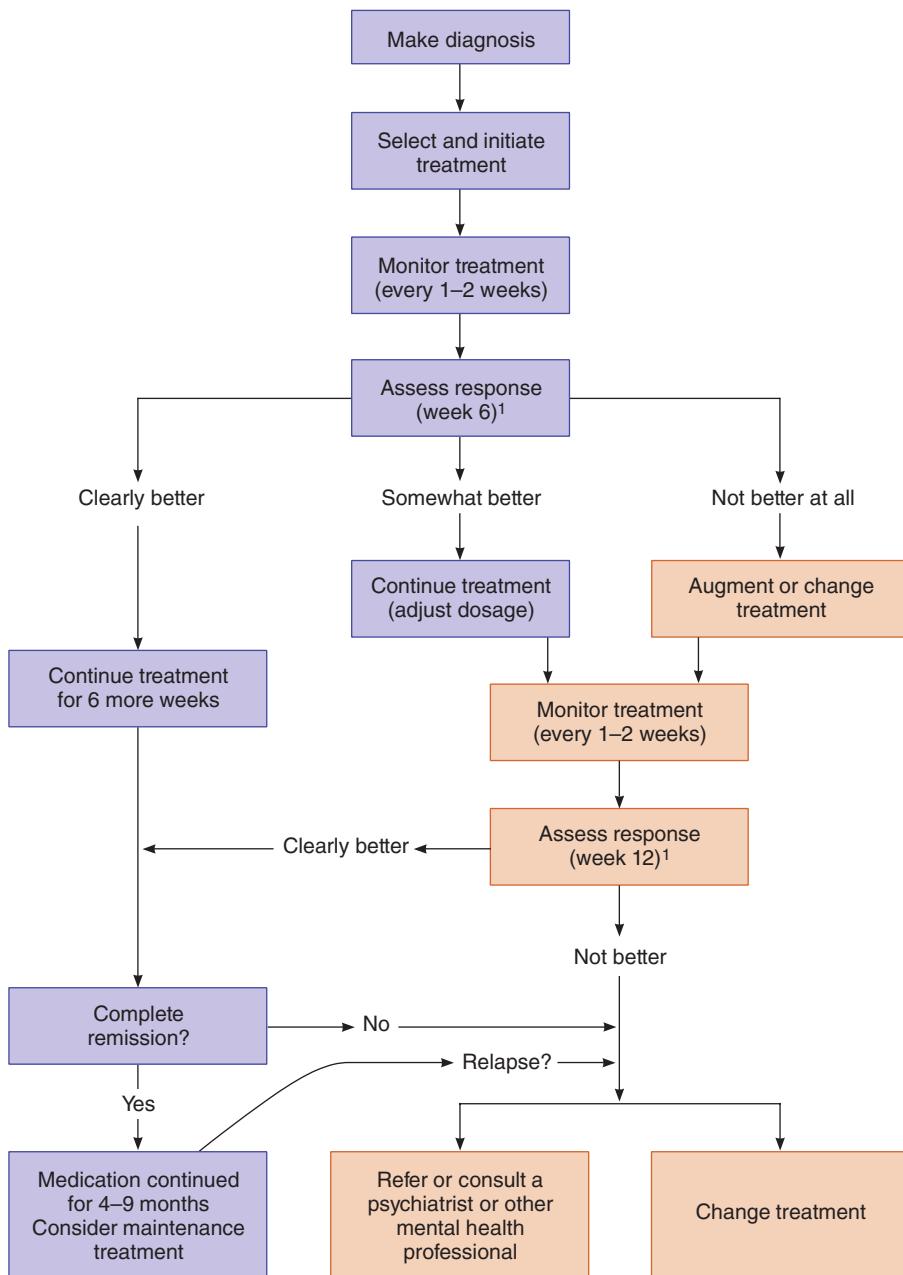
1. SSRIs, SNRIs, and atypical antidepressants—SSRIs include fluoxetine, sertraline, paroxetine, fluvoxamine, and citalopram and its enantiomer escitalopram (Table 25–7). The chief advantages of these agents are that they are generally well tolerated, the starting dose is typically a therapeutic dose for most patients, and they have much lower lethality in overdose compared to TCAs or MAO inhibitors. (Notably, citalopram carries a warning regarding QT prolongation in doses above 40 mg, and 20 mg is considered the maximum dose for patients older than 60 years. There is no similar FDA warning for escitalopram.) The SNRIs include venlafaxine, desvenlafaxine, duloxetine, milnacipran, and levomilnacipran. In addition to possessing the strong serotonin reuptake blocking properties of the SSRIs, the SNRIs are also norepinephrine reuptake blockers. The combined serotonergic-noradrenergic properties of these medications may provide benefits in pain conditions such as neuropathy and fibromyalgia as well as conditions such as stress incontinence. The atypical antidepressants are bupropion, nefazodone, trazodone, vilazodone, vortioxetine, and

Table 25–7. Commonly used antidepressant medications (listed in alphabetical order within classes).

Medication	Usual Daily Oral Dose (mg)	Usual Daily Maximum Dose (mg)	Sedative Effects ¹	Anticholinergic Effects ¹	Cost per Unit	Cost for 30 Days of Treatment Based on Maximum Dosage ²
SSRIs						
Citalopram (Celexa)	20	40	< 1	1	\$0.14/40 mg	\$4.20
Escitalopram (Lexapro)	10	20	< 1	1	\$0.29/20 mg	\$8.70
Fluoxetine (Prozac, Sarafem)	5–40	80	< 1	< 1	\$2.40/20 mg	\$288.00
Fluvoxamine (Luvox)	100–300	300	1	< 1	\$2.63/100 mg	\$236.70
Paroxetine (Paxil)	20–30	50	1	1	\$2.64/20 mg	\$161.10
Sertraline (Zoloft)	50–150	200	< 1	< 1	\$0.55/100 mg	\$33.00
SNRIs						
Desvenlafaxine (Pristiq)	50	100	1	< 1	\$11.47/100 mg	\$344.10
Duloxetine (Cymbalta)	40	60	2	3	\$1.92/60 mg	\$57.60
Levomilnacipran (Fetzima)	40	120	1	1	\$17.32/80 mg	\$519.60
Milnacipran (Savella)	100	200	1	1	\$8.42/100 mg	\$505.20
Venlafaxine XR (Effexor)	150–225	225	1	< 1	\$0.63/75 mg	\$56.70
Tricyclic and Clinically Similar Compounds						
Amitriptyline (Elavil)	150–250	300	4	4	\$2.14/150 mg	\$128.40
Amoxapine (Asendin)	150–200	400	2	2	\$1.98/100 mg	\$237.60
Clomipramine (Anafranil)	100	250	3	3	\$1.48/75 mg	\$177.60
Desipramine (Norpramin)	100–250	300	1	1	\$5.74/100 mg	\$516.60
Doxepin (Sinequan)	150–200	300	4	3	\$1.97/100 mg	\$177.30
Imipramine (Tofranil)	150–200	300	3	3	\$1.16/50 mg	\$219.60
Maprotiline (Ludiomil)	100–200	300	4	2	\$2.34/75 mg	\$280.80
Nortriptyline (Aventyl, Pamelor)	100–150	150	2	2	\$0.29/75 mg	\$17.40
Protriptyline (Vivactil)	15–40	60	1	3	\$3.30/10 mg	\$594.00
Trimipramine (Surmontil)	75–200	200	4	4	\$9.44/100 mg	\$566.40
Monoamine Oxidase Inhibitors						
Phenelzine (Nardil)	45–60	90	\$0.84/15 mg	\$151.20
Selegiline transdermal (Emsam)	6 (skin patch)	12	\$73.79/6 mg patch	\$2213.70
Tranylcypromine (Parnate)	20–30	50	\$3.60/10 mg	\$540.00
Other Compounds						
Bupropion SR (Wellbutrin SR)	300	400 ³	< 1	< 1	\$3.59/200 mg	\$215.40
Bupropion XL (Wellbutrin XL)	300 ⁴	450 ⁴	< 1	< 1	\$0.55/300 mg	\$32.10
Mirtazapine (Remeron)	15–45	45	4	2	\$2.77/30 mg	\$84.90
Nefazodone (Serzone)	150–600	600	3	1	\$4.98/200 mg	\$448.20
Trazodone (Desyrel)	100–300	400	4	< 1	\$0.21/100 mg	\$25.60
Vilazodone (Viibryd)	10–40	40	1	1	\$12.00/40 mg	\$360.00
Vortioxetine (Brintellix)	10	20	< 1	< 1	\$16.92/20 mg	\$507.60

¹1, weak effect; 4, strong effect.²Average wholesale price (AWP) for AB-rated generic when available) for quantity listed. Source: IBM Micromedex Red Book (electronic version) IBM Watson Health, Greenwood, CO, USA. Available at <https://www.micromedexsolutions.com> (cited April 18, 2021). AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions.³200 mg twice daily.⁴Wellbutrin XL is a once-daily form of bupropion. Bupropion is still available as immediate release, and, if used, no single dose should exceed 150 mg.

SNRIs, serotonin norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.



¹Times of assessment (weeks 6 and 12) rest on very modest data. It may be necessary to revise the treatment plan earlier for patients not responding at all.

▲ **Figure 25–2.** Overview of treatment for depression. (Reproduced from Agency for Health Care Policy and Research: Depression in Primary Care. Vol. 2: Treatment of Major Depression. United States Department of Health and Human Services, 1993.)

mirtazapine (Table 25–7). All of these antidepressants are effective in the treatment of depression, both typical and atypical. The SSRI medications have been effective in the treatment of panic disorder, bulimia, GAD, OCD, and PTSD.

Most of the medications in this group tend to be activating and are given in the morning so as not to interfere

with sleep. Some patients, however, may have sedation, requiring that the medication be given at bedtime. This reaction occurs most commonly with paroxetine, fluvoxamine, and mirtazapine. The SSRIs can be given in once-daily dosage. Nefazodone and trazodone are usually given twice daily. Bupropion and venlafaxine are available in extended-release formulations and can be given once daily.

There is usually some *delay in response*; fluoxetine, for example, requires 2–6 weeks to act in depression, 4–8 weeks to be effective in panic disorder, and 6–12 weeks in treatment of OCD. The starting dose (10 mg) is given for 1 week before increasing to the average daily oral dose of 20 mg for depression, while OCD may require up to 80 mg daily. Some patients, particularly the elderly, may tolerate and benefit from as little as 10 mg/day or every other day. The other SSRIs have shorter half-lives and a lesser effect on hepatic enzymes, which reduces their impact on the metabolism of other medications (thus not increasing significantly the serum concentrations of other medications as much as fluoxetine). The shorter half-lives also allow for more rapid clearing if adverse side effects appear. Venlafaxine appears to be more effective with doses greater than 200 mg/day orally, although some individuals respond to doses as low as 75 mg/day.

The side effects common to these medications are headache, nausea, tinnitus, insomnia, and nervousness. Akathisia has been common with the SSRIs; other extrapyramidal symptoms (eg, dystonias) have occurred infrequently but particularly in withdrawal states. Because SSRIs affect platelet serotonin levels, abnormal bleeding can occur. Sertraline and citalopram appear to be the safest agents in this class when used with warfarin. Sexual side effects of erectile dysfunction, retrograde ejaculation, and dysorgasmia are very common with the SSRIs. Oral phosphodiesterase-5 inhibitors (such as sildenafil, 25–50 mg; tadalafil, 5–20 mg; or vardenafil, 10–20 mg taken 1 hour prior to sexual activity) can improve erectile dysfunction in some patients and have been shown to improve other SSRI-induced sexual dysfunction in both men and women. Adjunctive bupropion (75–150 mg orally daily) may also enhance sexual arousal. Cyproheptadine, 4 mg orally prior to sexual activity, may be helpful in countering drug-induced anorgasmia but also is quite sedating and may counter the therapeutic benefits of SSRIs as well. Taking a “drug holiday,” ie, skipping a day of medication periodically when sexual activity is anticipated, can also decrease sexual side effects. The SSRIs are strong serotonin uptake blockers and may in high dosage or in combination with MAO inhibitors, including the antiparkinsonian drug selegiline, cause a **“serotonin syndrome.”** This syndrome is manifested by rigidity, hyperthermia, autonomic instability, myoclonus, confusion, delirium, and coma. This syndrome can be a particularly troublesome problem in the elderly. Research indicates that SSRIs are safer agents to use than TCAs in patients with cardiac disease; the SSRI sertraline is a safe and effective antidepressant treatment in patients with acute myocardial infarction or unstable angina.

Withdrawal symptoms, including dizziness, paresthesias, dysphoric mood, agitation, and a flu-like state, have been reported for the shorter-acting SSRIs and SNRIs but may occur with other classes including the TCAs and MAO inhibitors. These medications should be discontinued gradually over a period of weeks or months to reduce the risk of withdrawal phenomena.

Most studies show that SSRIs are *not* associated with birth defects. Paroxetine has some association with a fetal heart defect and should be avoided in favor of other SSRIs

during pregnancy. Maternal major mood disorder in pregnancy by itself carries its own risks to the mother and fetus and has been linked to low birth weight and preterm delivery. Postpartum effects of prenatal depression have not been studied. The decision to use SSRIs and other psychotropic agents during pregnancy and postpartum must be a collaborative decision based on a thorough risk-benefit analysis for each individual.

Venlafaxine lacks significant anticholinergic side effects. Nausea, nervousness, and profuse sweating appear to be the major side effects. Venlafaxine appears to have few drug-drug interactions. It does require monitoring of blood pressure because dose-related hypertension may develop in some individuals. Venlafaxine prescribing in the United Kingdom has been restricted to psychiatrists. Venlafaxine appears to carry a greater risk of lethal arrhythmias in instances of overdose relative to the SSRIs, but less risk than with the TCAs. Desvenlafaxine, a newer form of the medication, is started at its target dose of 50 mg/day orally and does not require upward titration although higher doses have been well studied and some patients benefit from 100 mg/day. Duloxetine may also result in small increases in blood pressure. Common side effects include dry mouth, dizziness, and fatigue. Inhibitors of 1A2 and 2D6 may increase duloxetine levels with a risk of toxicity. Milnacipran, approved for the treatment of fibromyalgia, and levomilnacipran, approved for the treatment of major depression, carry many of the side effects common to other SNRIs including a mild tachycardia, hypertension, sexual side effects, mydriasis, urinary constriction, and occasional abnormal bleeding. Levomilnacipran is started at 20 mg/day orally then increased to 40 mg/day after 2–3 days. The target dose is 40–120 mg given once daily. Milnacipran is typically started at 12.5 mg/day orally, titrated to 12.5 mg twice daily after 2 days, and then to 25 mg twice daily after 7 days. The target dose is typically 100–200 mg/day given in two divided doses. While not approved for the treatment of major depression, the evidence suggests that milnacipran, like levomilnacipran, is an effective antidepressant agent.

Nefazodone appears to lack the anticholinergic effects of the TCAs and the agitation sometimes induced by SSRIs. Nefazodone should not be given with terfenadine, astemizole, or cisapride, which are not commercially available in the United States. Because nefazodone inhibits the liver's cytochrome P450 3A4 isoenzymes, concurrent use of these medications can lead to serious QT prolongation, ventricular tachycardia, or death. Through the same mechanism of enzyme inhibition, nefazodone can elevate cyclosporine levels sixfold to tenfold. Nefazodone carries an FDA warning given its association with liver failure in rare cases. Pretreatment and ongoing monitoring of liver biochemical enzymes are indicated.

Mirtazapine is thought to enhance central noradrenergic and serotonergic activity with minimal sexual side effects compared with the SSRIs. Its action as a potent antagonist of histaminergic receptors may make it a useful agent for patients with depression and insomnia. It is also an effective antiemetic due to its antagonism of the 5-HT₃ receptor. Its most common adverse side effects include

somnolence, increased appetite, weight gain, lipid abnormalities, and dizziness. The labeling for mirtazapine indicated that agranulocytosis was seen in 2 of 2796 patients in premarketing studies. An association of agranulocytosis or a clinically significant neutropenia with the medication appears to be modest. Although it is metabolized by P450 isoenzymes, it is not an inhibitor of this system. It is given in a single oral dose at bedtime starting at 15 mg and titrated up to 45 mg with some evidence that 30 mg may be optimal for most people.

Vortioxetine is an antidepressant that blocks serotonin reuptake, is a partial agonist of the 5-HT_{1A} receptor, and affects a variety of other serotonin receptor sites. The side effects attributed to its serotonergic effects include gastrointestinal upset and sexual dysfunction. Vortioxetine has demonstrated efficacy in improving some cognitive symptoms of depression and received regulatory approval for this indication in Europe and the United States. Vortioxetine is typically dosed at 10 mg/day orally and may be increased to 20 mg/day.

2. Tricyclic antidepressants (TCAs) and clinically similar medications—TCAs were the mainstay of medication therapy for depression for many years. They have also been effective in panic disorder, pain syndromes, and anxiety states. Specific ones have been studied and found to be effective in OCD (clomipramine), enuresis (imipramine), psychotic depression (amoxapine), and reduction of craving in cocaine withdrawal (desipramine).

TCAs are characterized more by their similarities than by their differences. They tend to affect both serotonin and norepinephrine reuptake; some medications act mainly on the former and others principally on the latter neurotransmitter system. Individuals receiving the same dosages vary markedly in therapeutic drug levels achieved (elderly patients require smaller doses), and determination of plasma drug levels is helpful when clinical response has been disappointing. Nortriptyline is usually effective when plasma levels are between 50 and 150 ng/mL; imipramine at plasma levels of 200–250 ng/mL; and desipramine at plasma levels of 100–250 ng/mL. High blood levels are not more effective than moderate levels and may be counterproductive (eg, delirium, seizures). Patients with gastrointestinal side effects benefit from plasma level monitoring to assess absorption of the drug. Most TCAs can be given in a single dose at bedtime, starting at fairly low doses (eg, nortriptyline 25 mg orally) and increasing by 25 mg every several days as tolerated until the therapeutic response is achieved (eg, nortriptyline, 100–150 mg) or to maximum dose if necessary (eg, nortriptyline, 150 mg). *The most common cause of treatment failure is an inadequate trial.* A full trial consists of giving a therapeutic daily dosage for at least 6 weeks. Because of marked anticholinergic and sedating side effects, clomipramine is started at a low dose (25 mg/day orally) and increased slowly in divided doses up to 100 mg/day, held at that level for several days, and then gradually increased as necessary up to 250 mg/day. The TCAs have anticholinergic side effects to varying degrees (amitriptyline 100 mg is equivalent to atropine 5 mg). One must be particularly wary of the effect in elderly men with prostatic hyperplasia. The anticholinergic effects also

predispose to other medical problems such as constipation, confusion, heat stroke, or dental problems from xerostomia. Orthostatic hypotension is fairly common, is not dose-dependent, and may not remit with time on medication; this may predispose to falls and hip fractures in the elderly.

Cardiac effects of the TCAs are functions of the anticholinergic effect, direct myocardial depression, quinidine-like effect, and interference with adrenergic neurons. These factors may produce altered rate, rhythm, and contractility, particularly in patients with preexisting cardiac disease, such as bundle-branch or bifascicular block. Even relatively small overdoses (eg, 1500 mg of imipramine) have resulted in lethal arrhythmias. Electrocardiographic changes range from benign ST segment and T wave changes and sinus tachycardia to a variety of complex and serious arrhythmias, the latter requiring a change in medication. Because TCAs have class I antiarrhythmic effects, they should be used with caution in patients with ischemic heart disease, arrhythmias, or conduction disturbances. SSRIs or the atypical antidepressants are better initial choices for this population.

TCAs lower the seizure threshold, so this is of particular concern in patients with a propensity for seizures. Loss of libido and erectile, ejaculatory, and orgasmic dysfunction are common and can compromise compliance. Trazodone rarely causes priapism (1 in 9000), but when it occurs, it requires treatment within 12 hours (epinephrine 1:1000 injected into the corpus cavernosum). Delirium, agitation, and mania are infrequent complications of the TCAs but can occur. Sudden discontinuation of some of these medications can produce “cholinergic rebound,” manifested by headaches and nausea with abdominal cramps. Overdoses of TCAs are often serious because of the narrow therapeutic index and quinidine-like effects (see Chapter 38).

3. Monoamine oxidase inhibitors—The MAO inhibitors are generally used as third-line medications for depression (after a failure of SSRIs, SNRIs, TCAs, or the atypical antidepressants) because of the dietary and other restrictions required (Table 25–8). They should be considered third-line medications for refractory panic disorder as well as depression; however, this hierarchy has become more flexible since MAO inhibitor skin patches (selegiline) have become available. They deliver the MAO inhibitor to the bloodstream bypassing the gastrointestinal tract so that dietary restrictions are not necessary in the lowest dosage strength (6 mg/24 h).

The MAO inhibitors commonly cause symptoms of orthostatic hypotension (which may persist) and sympathomimetic effects of tachycardia, sweating, and tremor.

Table 25–8. Principal dietary restrictions in MAOI use.

1. Cheese, except cream cheese and cottage cheese and fresh yogurt
2. Fermented or aged meats such as bologna, salami
3. Broad bean pods such as Chinese bean pods
4. Liver of all types
5. Meat and yeast extracts
6. Red wine, sherry, vermouth, cognac, beer, ale
7. Soy sauce, shrimp paste, sauerkraut

MAOI, monoamine oxidase inhibitor.

Nausea, insomnia (often associated with intense afternoon drowsiness), and sexual dysfunction are common. Zolpidem 5–10 mg orally at bedtime can ameliorate MAO-induced insomnia. Central nervous system effects include agitation and toxic psychoses. *Dietary limitations* (see Table 25–8) and abstinence from medication products containing phenylpropanolamine, phenylephrine, meperidine, dextromethorphan, and pseudoephedrine are mandatory for MAO-A type inhibitors (those marketed for treatment of depression), since the reduction of available MAO leaves the patient vulnerable to exogenous amines (eg, tyramine in foodstuffs).

4. Other medications and those under investigation—

Dextroamphetamine (5–30 mg/day orally) and methylphenidate (10–45 mg/day orally) may be effective for the short-term treatment of some depressive symptoms in medically ill and geriatric patients. The stimulants are notable for rapid onset of action (hours) and a paucity of side effects (tachycardia, agitation) in most patients. They are usually given in two divided doses early in the day (eg, 7 am and noon) so as to avoid interfering with sleep. These agents may also be useful as adjunctive agents in refractory depression. Intravenous infusion of the dissociative anesthetic ketamine has been shown to lead to a rapid improvement in depressive symptoms in 50–70% of patients with depression. The effects of a single treatment are short-lived (about 3–7 days). Ketamine acts both through the glutamate system as well as the opioid system. Esketamine nasal spray has been approved by the FDA for the treatment of depression for patients who have been inadequately treated by two other antidepressant medications. However, there are ongoing concerns about long-term use of esketamine or ketamine, including the risk of abuse and longer-term impacts on mood and suicidality. Other NMDA antagonists and opioid system agents continue to be evaluated in the treatment of resistant depression.

Allopregnanolone, a neurosteroid, is an allosteric modulator of GABA-a receptors and is approved for the treatment of postpartum depression. Like ketamine, allopregnanolone is administered intravenously, and the antidepressant effects are rapid. An allopregnanolone infusion is given over 60 hours in a health care facility and was significantly more effective than placebo in treating postpartum depression by the end of the 2.5-day infusion, and benefits were sustained for the 30 days of the study period in three registration trials. The most common side effects of allopregnanolone are headache, dizziness, and somnolence. There is a rare side effect of loss of consciousness that requires the infusion be monitored in a health care facility. There is good reason to believe that GABA-a modulators will be useful in other types of depression, including for addressing anxiety and insomnia in patients with more severe depression. Several orally active GABA-a modulators are in development.

5. Switching and combination therapy—If the therapeutic response has been poor after an adequate trial with the chosen medication, the diagnosis should be reassessed. Assuming that the trial has been adequate and the diagnosis is correct, a trial with a second medication is

appropriate. In switching from one group to another, an adequate “washout time” must be allowed. This is critical in certain situations—eg, in switching from a MAO inhibitor to a TCA, allow 2–3 weeks between stopping one medication and starting another; in switching from an SSRI to a MAO inhibitor, allow 4–5 weeks for fluoxetine and at least 2 weeks for other SSRIs. In switching within groups—eg, from one TCA to another (amitriptyline to desipramine, etc)—no washout time is needed, and one can rapidly decrease the dosage of one medication while increasing the other. In clinical practice, adjunctive treatment with lithium, buspirone, or thyroid hormone may be helpful in depression. The adjunctive use of low-dose atypical antipsychotics such as aripiprazole, olanzapine, and quetiapine in the treatment of patients with refractory depression is supported by research. The side effect risk is the same as when treating psychosis. Adding an atypical agent requires monitoring body mass index, lipids, and glucose. Combining two antidepressants, or adding an antipsychotic to an antidepressant requires caution and is usually reserved for clinicians who feel comfortable managing this or after psychiatric consultation.

6. Maintenance and tapering—When clinical relief of symptoms is obtained, medication is continued for 12 months in the effective maintenance dosage, which is the dosage required in the acute stage. The full dosage should be continued indefinitely when the individual has a first episode before age 20 or after age 50, is over age 40 with two episodes, has at least one episode after age 50, or has had three episodes at any age. *Major depression generally should be considered a chronic/intermittent disease with most patients having relapses in time and some patients never fully recovering from a depressive episode.* If the medication is being tapered, it should be done gradually over several months, monitoring closely for relapse.

7. Drug interactions—Interactions with other medications are listed in Table 25–9.

8. Electroconvulsive therapy—ECT causes a generalized central nervous system seizure (peripheral evidence of the convulsion is not necessary) by means of electric current. The key objective is to exceed the seizure threshold, which can be accomplished by a variety of means. The mechanism of action is not known, but it is thought to involve major neurotransmitter responses at the cell membrane.

ECT is the most effective (about 45–85% remission rate) treatment of severe depression. In more treatment-resistant depression, remission rates from ECT are lower (around 48%). It is particularly effective for the delusions and agitation commonly seen with depression in the elderly. It is indicated when medical conditions preclude the use of antidepressants, nonresponsiveness to these medications, and extreme suicidality. Comparative controlled studies of ECT in severe depression show that it is more effective than pharmacotherapy. It is also effective in the treatment of mania and catatonia. It has also been shown to be helpful in chronic schizophrenic disorders when clozapine alone is not fully effective.

The most common side effects of ECT are memory disturbance and headache. Memory loss or confusion is usually related to the number and frequency of

Table 25–9. Antidepressant drug interactions with other medications (listed in alphabetical order within classes).

Medication	Effects
Tricyclic and Other Non-MAOI Antidepressants	
Antacids	Decreased absorption of antidepressants
Anticoagulants	Increased hypoprothrombinemic effect
Cimetidine	Increased antidepressant blood levels and psychosis
Clonidine	Decreased antihypertensive effect
Digitalis	Increased incidence of heart block
Disulfiram	Increased antidepressant blood levels
Haloperidol	Increased antidepressant levels
Insulin	Decreased blood sugar
Lithium	Increased lithium levels with fluoxetine
Methyldopa	Decreased antihypertensive effect
Other anticholinergic medications	Marked anticholinergic responses
Phenytoin	Increased blood levels
Procainamide	Decreased ventricular conduction
Procarbazine	Hypertensive crisis
Propranolol	Increased hypotension
Quinidine	Decreased ventricular conduction
Rauwolffia derivatives	Increased stimulation
Sedatives	Increased sedation
Sympathomimetic medications	Increased vasoconstrictor effect
Terfenadine, ¹ astemizole, ¹ cisapride ¹	Torsades de pointes
MAOIs	
Antihistamines	Increased sedation
Belladonna-like medications	Increased blood pressure
Dextromethorphan	Same as meperidine
Guanethidine	Decreased blood pressure
Insulin	Decreased blood sugar
Levodopa	Increased blood pressure
Meperidine	Increased agitation, serotonin syndrome, death
Methyldopa	Decreased blood pressure
Pseudoephedrine	Hypertensive crisis (increased blood pressure)
Reserpine	Increased blood pressure/hypertensive crisis
Succinylcholine	Increased neuromuscular blockade
Sulfonylureas	Decreased blood sugar
Sympathomimetic medications	Increased blood pressure/hypertensive crisis
SSRIs, SNRIs, triptans	Serotonin syndrome, death

¹Terfenadine, astemizole, and cisapride are not commercially available in the United States.

MAOIs, monoamine oxidase inhibitors; SNRIs, serotonin norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.

ECT treatments and proper oxygenation during treatment. Unilateral ECT is associated with less memory loss than bilateral ECT. Both anterograde and retrograde memory loss may occur, but short-term anterograde memory loss is more common. While some memory deficits may persist, memory loss tends to improve in a few weeks after the last ECT treatment.

Increased intracranial pressure is a contraindication. Other problems such as cardiac disorders, aortic aneurysms, bronchopulmonary disease, and venous thrombosis must be evaluated in light of the severity of the medical problem versus the need for ECT. Serious complications arising from ECT occur in less than 1 in 1000 cases. Most of these problems are cardiovascular or respiratory in nature (eg, aspiration of gastric contents, arrhythmias, myocardial infarction). Poor patient understanding and lack of acceptance of the technique by the public are some of the biggest obstacles to the use of ECT.

9. Phototherapy—Phototherapy is used in major depression with seasonal onset. It consists of indirect eye exposure to a light source of greater than 2500 lux for 2 hours daily or 10,000 lux for 20 minutes daily to increase the photoperiod of the day. Light visors are an adaptation that provides greater mobility and an adjustable light intensity but may not be as effective. The dosage varies, with some patients requiring morning and night exposure. One effect is alteration of bio-rhythm through melatonin mechanisms.

10. Repetitive transcranial magnetic stimulation—Repetitive transcranial magnetic stimulation (rTMS) is used to treat nonpsychotic treatment-resistant depression and involves the application of electromagnetic pulses to the dorsolateral prefrontal cortex. Its use in depression is approved by the FDA for individuals who have not tolerated or responded to at least one or more standard antidepressant medications. It is usually delivered in a course of 30 sessions over 6 weeks. rTMS neither requires general anesthesia nor is it associated with cognitive side effects. Several meta-analyses have demonstrated that in nonpsychotic depression, rTMS is noninferior to ECT. There is a small risk of seizure (1:30,000 in post market research), and this is due primarily to operator error. The most common side effects are scalp sensitivity under the coil and transient headache.

11. Other treatments—Vagus nerve stimulation has shown promise in about one-third of extremely refractory cases and is approved by the FDA but has not been approved by insurers. Data have demonstrated that the effects plateau around 18 months to 2 years and are durable at 5 years. Deep brain stimulation continues to be explored for the treatment of refractory depression but two multisite randomized controlled studies in two separate targets (subgenual cingulate and ventral capsule/ventral striatum) have not shown success to date. There has been one successful trial but the study methodology was a derivation of the traditional randomized controlled trial. This is still considered an experimental approach, and the appropriate target and methodology are unknown.

B. Psychological

It is often challenging to engage an individual in penetrating psychotherapeutic endeavors during the acute stage of

a severe depression. While medications may be taking effect, a supportive and behavioral approach to strengthen existing coping mechanisms and appropriate consideration of the patient's continuing need to function at work, to engage in recreational activities, etc, are necessary as the severity of the depression lessens. Therapy during or just after the acute stage may focus on coping techniques, with some practice of alternative choices. Depression-specific psychotherapies help improve self-esteem, increase assertiveness, and lessen dependency. Interpersonal psychotherapy for depression has shown efficacy in the treatment of acute depression, helping patients master interpersonal stresses and develop new coping strategies. Cognitive behavioral therapy for depression addresses patients' patterns of negative thoughts, called cognitive distortions, which lead to feelings of depression and anxiety. Treatment usually includes homework assignments such as keeping a journal of cognitive distortions and of positive responses to them. *The combination of medication therapy plus interpersonal psychotherapy or cognitive behavioral therapy is generally more effective than either modality alone.* It is sometimes helpful to involve the spouse or other significant family members early in treatment. Mindfulness-based cognitive therapy has reduced relapse rates in several randomized controlled trials. In two studies, it was as effective as maintenance medication in preventing relapse. This therapy incorporates meditation and teaches patients to distance themselves from depressive thinking.

C. Social

Flexible use of appropriate social services can be of major importance in the treatment of depression. Since alcohol abuse is often associated with depression, early involvement in alcohol treatment programs such as Alcoholics Anonymous can be important to future success (see Alcohol Use Disorder [Alcoholism]). The structuring of daily activities during severe depression is often quite difficult for the patient, and loneliness is often a major factor. The help of family, employer, or friends is often necessary to mobilize the patient who experiences no joy in daily activities and tends to remain uninvolved and to deteriorate. Insistence on sharing activities will help involve the patient in simple but important daily functions. In some severe cases, the use of day treatment centers or support groups of a specific type (eg, mastectomy groups) is indicated. It is not unusual for a patient to have multiple legal, financial, and vocational problems requiring legal and vocational assistance.

D. Behavioral

When depression is a function of self-defeating coping techniques such as passivity, the role-playing approach can be useful. Behavioral techniques, including desensitization, may be used in problems such as phobias where depression is a by-product. When depression is a regularly used interpersonal style, behavioral counseling to family members or others can help in extinguishing the behavior in the patient. Behavioral activation, a technique of motivating depressed patients to begin engaging in pleasurable activities, has been shown to be a useful depression-specific psychotherapy. Exercise, especially aerobic and supervised

by exercise professionals, has evidence in improving depressive symptoms.

► Treatment of Bipolar Disorder, Manic & Depressive Episodes

Acute manic or hypomanic symptoms will respond to the mood stabilizers lithium or valproic acid after several days of treatment. Antipsychotics may be used as well for mania. High-potency benzodiazepines (eg, clonazepam) may also be useful adjuncts in managing the agitation and sleep disturbance that are features of manic and hypomanic episodes.

A. Antipsychotics

Acute manic symptoms may be treated initially with a second-generation antipsychotic such as olanzapine, (eg, 5–20 mg orally), risperidone (2–3 mg orally), or aripiprazole (15–30 mg) in conjunction with a benzodiazepine if indicated. Alternatively, when behavioral control is immediately necessary, olanzapine in an injectable form (2.5–10 mg intramuscularly) or haloperidol, 5–10 mg orally or intramuscularly repeated as needed until symptoms subside, may be used. The dosage of the antipsychotic may be gradually reduced after lithium or another mood stabilizer is started. Olanzapine, quetiapine, ziprasidone, aripiprazole, and the long-acting injectable risperidone are approved as maintenance treatments for bipolar disorder to prevent subsequent cycles of both mania and depression.

B. Valproic Acid

Valproic acid (divalproex) is a first-line treatment for mania. This issue is particularly important in AIDS or other medically ill patients prone to dehydration or malabsorption with wide swings in serum lithium levels. Valproic acid has also been used effectively in panic disorder and migraine headache. Treatment is often started at a dose of 750 mg/day orally, and dosage is then titrated to achieve therapeutic serum levels. Oral loading in acutely manic bipolar patients in an inpatient setting (initiated at a dosage of 20 mg/kg/day) can safely achieve serum therapeutic levels in 2–3 days. Concomitant use of aspirin may increase valproate levels, carbamazepine or phenytoin may decrease valproate levels, while warfarin levels may be elevated by valproate. Gastrointestinal symptoms and weight gain are the main side effects. Liver enzyme biochemical tests, complete blood counts, glucose levels, and weight should be monitored at 2 weeks, 4 weeks, and 3 months initially and annually or more frequently thereafter based on clinical judgment. Significant teratogenic effects are a concern so pregnancy should be ruled out prior to initiation. In utero exposure to valproate has been associated with adversely affecting neural tube development in the fetus and there is an FDA warning to that effect. Thus, alternatives to valproate should be considered in women of child-bearing years who might become pregnant.

C. Lithium

Lithium significantly decreases the frequency and severity of both manic and depressive attacks in about 50–70% of patients and is FDA approved for maintenance and manic episodes.

In addition to its use in bipolar disorder, lithium is sometimes useful in the prophylaxis of recurrent unipolar depressions (perhaps undiagnosed bipolar disorder) and in lowering the risk of suicide. Lithium may ameliorate non-specific aggressive behaviors and dyscontrol syndromes. *Many patients with bipolar disease can be managed long-term with lithium alone*, although some will require continued or intermittent use of an antipsychotic or lamotrigine to help prevent depressive episodes. An excellent resource for information is the Lithium Information Center, <https://www.uwhealth.org/health/topic/multum/lithium/d00061a1.html>.

Before treatment, the clinical workup should include a medical history and physical examination; complete blood count; T₄, thyroid-stimulating hormone, blood urea nitrogen (BUN), serum creatinine, and serum electrolyte determinations; urinalysis; and electrocardiography (in patients over age 45 or with a history of cardiac disease).

1. Dosage—The common starting dosage of lithium carbonate is 300–900 mg daily, with trough blood levels measured after 4–5 days of treatment. A slow release form or units of different dosage may be used. Lithium citrate is available as a syrup. The dosage is that required to maintain blood levels in the therapeutic range. For acute manic episodes, this ranges from 0.8 mEq/L to 1.2 mEq/L. Although there is controversy about the optimal long-term maintenance dose, many clinicians reduce the acute level to 0.6–1 mEq/L in order to reduce side effects. The dose required to meet this need will vary in different individuals. Augmentation of antidepressants is usually achieved with lower blood levels. Once-a-day dosage is acceptable.

Lithium is readily absorbed, with peak serum levels occurring within 1–3 hours and complete absorption in 8 hours. Half of the total body lithium is excreted in 18–24 hours (95% in the urine). Blood for lithium levels should be drawn 12 hours after the last dose. Serum levels should be measured 4–7 days after initiation of treatment and changes in dose. For maintenance treatment, lithium levels should be monitored initially every 1–2 months but may be measured every 6–12 months in stable, long-term patients. Levels should be monitored more closely when there is any condition that causes volume depletion (eg, diarrhea, dehydration, use of diuretics).

2. Side effects—**Early side effects**, including mild gastrointestinal symptoms (take lithium with food and in divided doses), fine tremors (treat with propranolol, 20–60 mg/day orally, only if persistent), slight muscle weakness, and some degree of somnolence, can occur and are usually transient. Moderate polyuria (reduced renal responsiveness to ADH) and polydipsia (associated with increased plasma renin concentration) are often present. Potassium administration can blunt this effect, as may once-daily dosing of lithium. Weight gain (often a result of calories in fluids taken for polydipsia) and leukocytosis not due to infection can occur.

Thyroid side effects include goiter (3%; often euthyroid) and hypothyroidism (10%; concomitant administration of lithium and iodide or lithium and carbamazepine enhances the hypothyroid and goitrogenic effect of either medication). Most clinicians treat lithium-induced

hypothyroidism (more common in women) with thyroid hormone while continuing lithium therapy. Changes in the glucose tolerance test toward a diabetes-like curve, nephrogenic diabetes insipidus (usually resolving about 8 weeks after cessation of lithium therapy), nephrotic syndrome, edema, folate deficiency, and pseudotumor cerebri (ophthalmoscopy is indicated if there are complaints of headache or blurred vision) can occur. Thyroid and kidney function should be checked at 4- to 6-month intervals. Hypercalcemia and elevated parathyroid hormone levels occur in some patients. Electrocardiographic abnormalities (principally T wave flattening or inversion) may occur during lithium administration but are not of major clinical significance. Sinoatrial block may occur, particularly in the elderly. Other medications that prolong intraventricular conduction, such as TCAs, must be used cautiously in conjunction with lithium. Lithium impairs ventilatory function in patients with airway obstruction. Lithium alone does not have a significant effect on sexual function, but when combined with benzodiazepines (clonazepam in most symptomatic patients), it causes sexual dysfunction in about 50% of men. Lithium may precipitate or exacerbate psoriasis in some patients and can also cause acne. Most of these side effects subside when lithium is discontinued; when residual side effects exist, they are usually not serious.

Side effects from long-term lithium therapy include the development of cogwheel rigidity and, occasionally, other extrapyramidal signs. Lithium potentiates the parkinsonian effects of haloperidol. Lithium-induced delirium with therapeutic lithium levels is an infrequent complication usually occurring in the elderly and may persist for several days after serum levels have become negligible. Encephalopathy has occurred in patients receiving combined lithium and antipsychotic therapy and in those who have cerebrovascular disease, thus requiring careful evaluation of patients who develop neurotoxic signs at subtoxic blood levels.

Some reports have suggested that the long-term use of lithium may have adverse effects on kidney function (with interstitial fibrosis, tubular atrophy, or nephrogenic diabetes insipidus). Persistent polyuria should require an investigation of the kidney's ability to concentrate urine. A rise in serum creatinine levels is an indication for in-depth evaluation of kidney function and consideration of alternative treatments if the individual can tolerate a change. Incontinence has been reported in women, apparently related to changes in bladder cholinergic-adrenergic balance.

Prospective studies suggest that the overall risk imposed by lithium in pregnancy may be overemphasized. However, lithium exposure in early pregnancy does minimally increase the frequency of rare congenital anomalies, notably Ebstein and other major cardiovascular anomalies. For women who take psychotropic medications who become pregnant, the decision to make a change in medication is complex and requires informed consent regarding the relative risks to the patient and fetus. Indeed, the risk of untreated bipolar disorder carries its own risks for pregnancy. Mothers who take lithium should use formula to feed their newborn, since concentration in breast milk is one-third to half that in serum.

Frank toxicity usually occurs at blood lithium levels greater than 2 mEq/L. Because sodium and lithium are reabsorbed at the same loci in the proximal renal tubules, any sodium loss (diarrhea, use of diuretics, or excessive perspiration) increases lithium levels. Symptoms and signs include vomiting and diarrhea, the latter exacerbating the problem since more sodium is lost and more lithium is absorbed. Other symptoms and signs, some of which may not be reversible, include tremors, marked muscle weakness, confusion, dysarthria, vertigo, choreoathetosis, ataxia, hyperreflexia, rigidity, lack of coordination, myoclonus, seizures, opisthotonus, and coma. Toxicity is more severe in the elderly, who should be maintained on slightly lower serum levels. Lithium overdosage may be accidental or intentional or may occur because of poor monitoring. Significant overdoses of lithium are typically managed with hemodialysis since the medication is excreted completely by the kidneys.

See Chapter 38 for the treatment of patients with massive ingestions of lithium or blood lithium levels greater than 2.5 mEq/L.

3. Drug interactions—Patients receiving lithium should use diuretics with caution and only under close medical supervision. The thiazide diuretics cause increased lithium reabsorption from the proximal renal tubules, resulting in increased serum lithium levels (Table 25–10), and adjustment of lithium intake must be made to compensate for this. Reduce lithium dosage by 25–40% when the patient is receiving 50 mg of hydrochlorothiazide daily. Potassium-sparing diuretics (spironolactone, amiloride,

triamterene) may also increase serum lithium levels and require careful monitoring of lithium levels. Loop diuretics (furosemide, ethacrynic acid, bumetanide) do not appear to alter serum lithium levels. Concurrent use of lithium and angiotensin-converting enzyme inhibitors requires a 50–75% reduction in lithium intake, as does prolonged concurrent use of nonsteroidal anti-inflammatory medication.

D. Carbamazepine

Carbamazepine is used in the treatment of bipolar patients who cannot be satisfactorily treated with lithium (nonresponsive, excessive side effects, or rapid cycling). It is often effective at 800–1600 mg/day orally. It has also been used in the treatment of trigeminal neuralgias and alcohol withdrawal as well as in patients with behavioral dyscontrol. It has been used to treat residual symptoms in previous stimulant abusers (eg, PTSD with impulse control problems). Dose-related side effects include sedation and ataxia. Dosages start at 400–600 mg orally daily and are increased slowly to therapeutic levels. Skin rashes and a mild reduction in white count are common. SIADH occurs rarely. Nonsteroidal anti-inflammatory medications (except aspirin), the antibiotics erythromycin and isoniazid, the calcium channel blockers verapamil and diltiazem (but not nifedipine), fluoxetine, propoxyphene, and cimetidine all increase carbamazepine levels. Carbamazepine can be effective in conjunction with lithium, although there have been reports of reversible neurotoxicity with the combination. Carbamazepine stimulates hepatic microsomal enzymes and so tends to decrease levels of haloperidol and oral contraceptives. It also lowers T₄, free T₄, and T₃ levels. Cases of fetal malformation (particularly spina bifida) have been reported along with growth deficiency and developmental delay. Liver biochemical tests and complete blood counts should be monitored in patients taking carbamazepine. Genetic studies suggest that screening for the HLA-B1502 allele in the Han Chinese population and the HLA-A3101 allele in northern Europeans may help target individuals more susceptible to a serious rash. Oxcarbazepine, a derivative of carbamazepine, does not appear to induce its own metabolism, and is associated with fewer drug interactions, although it may impose a higher risk of hyponatremia. FDA-approved for partial seizures, oxcarbazepine may have efficacy in acute mania. It appears to be a safer alternative to carbamazepine due to its lower risk of hepatotoxicity.

E. Lamotrigine

Lamotrigine is thought to inhibit neuronal sodium channels and the release of the excitatory amino acids, glutamate and aspartate. It is FDA-approved for the maintenance treatment of bipolar disorder. Two double-blind studies support its efficacy in the treatment of acute bipolar depression as adjunctive therapy or as monotherapy, but several other controlled studies failed to demonstrate benefit. Likewise, lamotrigine has *not* proven effective in the management of acute mania. Its metabolism is inhibited by coadministration of valproic acid—doubling its

Table 25–10. Lithium interactions with other medications (listed in alphabetical order).

Medication	Effects
ACE inhibitors	↑ Lithium levels
Celecoxib	↑ Lithium levels
Fluoxetine	↑ Lithium levels
Ibuprofen	↑ Lithium levels
Indomethacin	↑ Lithium levels
Methyldopa	Rigidity, mutism, fascicular twitching
Osmotic diuretics (urea, mannitol)	↑ Lithium excretion
Phenylbutazone	↑ Lithium levels
Potassium-sparing diuretics (spironolactone, amiloride, triamterene)	↑ Lithium levels
Sodium bicarbonate	↑ Lithium excretion
Succinylcholine	↑ Duration of action of succinylcholine
Theophylline, aminophylline	↑ Lithium excretion
Thiazide diuretics	↑ Lithium levels
Valproic acid	↓ Lithium levels

ACE, angiotensin-converting enzyme.

half-life—and accelerated by hepatic enzyme-inducing agents such as carbamazepine. More frequent mild side effects include headache, dizziness, nausea, and diplopia. Rash occurring in 10% of patients may be an indication for immediate cessation of dosing, since lamotrigine has been associated with Stevens-Johnson syndrome (1:1000) and, rarely, toxic epidermal necrolysis. The medication should be stopped for a rash associated with systemic symptoms including fever, lymphadenopathy, and oral mucosa ulcerations, and the patient sent to an emergency department. Any new rash associated with lamotrigine use should be evaluated by a dermatologist. Dosing starts at 25–50 mg/day orally and is titrated upward slowly to decrease the likelihood of rash. Slower titration and a lower total dose are indicated for patients taking valproic acid.

► Prognosis

Most depressive episodes are usually time-limited, and the prognosis with treatment is good if a pathologic pattern of adjustment does not intervene. Major affective disorders frequently respond well to a full trial of medication treatment. However, at least 20% of patients will have a more chronic illness lasting 2 or more years. Many patients do not sustain a complete remission of symptoms and most depressive episodes recur. *At least 80% of patients who have a single major depressive episode will have one or more recurrences within 15 years of the index episode.* Many patients, therefore, require long-term maintenance therapy with antidepressants.

Mania has a good prognosis with adequate treatment, although patient adherence to treatment is often quite challenging. Few effective medications exist for bipolar depression, which include quetiapine, lurasidone, cariprazine, and the combination of fluoxetine and olanzapine. Many patients with bipolar disorder require treatment with two or more medications such as lithium, antipsychotics, and sleeping agents. Breakthrough manic or depressive episodes are common, even with adherence to maintenance treatments, although maintenance therapy lessens the risk of recurrent episodes.

Bueno-Notivol J et al. Prevalence of depression during the COVID-19 outbreak: a meta-analysis of community-based studies. *Int J Clin Health Psychol.* 2021;21:100196. [PMID: 32904715]

Cipriani A et al. Comparative efficacy and acceptability of 21 anti-depressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet.* 2018;391:1357. [PMID: 29477251]

Daly EJ et al. Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: a randomized clinical trial. *JAMA Psychiatry.* 2018;75:139. [PMID: 29282469]

Furukawa TA et al. Optimal dose of selective serotonin reuptake inhibitors, venlafaxine, and mirtazapine in major depression: a systematic review and dose-response meta-analysis. *Lancet Psychiatry.* 2019;6:601. [PMID: 31178367]

Leader LD et al. Brexanolone for postpartum depression: clinical evidence and practical considerations. *Pharmacotherapy.* 2019;39:1105. [PMID: 31514247]

Molero P et al. Antidepressant efficacy and tolerability of ketamine and esketamine: a critical review. *CNS Drugs.* 2018;32:411. [PMID: 29736744]

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

ESSENTIALS OF DIAGNOSIS

- ▶ Persistent patterns of inability to sustain attention, excessive motor activity/restlessness/impulsivity, or both.
- ▶ Symptoms interfere with daily functioning.
- ▶ Symptoms began prior to age 12 and in at least two settings (ie, school/work, home, with friends/family).

► Clinical Findings

While attention-deficit/hyperactivity disorder (ADHD) begins in childhood, symptoms persist into adulthood in approximately two-thirds of patients, with half of those still requiring medication to aid in their functioning. The prevalence of ADHD in adults is estimated to be 4–5%. ADHD is never diagnosed in some patients during childhood because they may not have presented for assessment at that time or were able to compensate for symptoms at the time. *The specific presenting symptoms in adulthood tend to be inattention, restlessness, and impulsivity, whereas hyperactivity has often improved.* At least five inattention symptoms (such as making careless mistakes, being easily sidetracked, trouble keeping deadlines or with organization, losing belongings, being forgetful in daily chores/tasks) are required to meet criteria for this subtype of ADHD, or five hyperactivity/impulsivity symptoms (such as feeling restless and leaving a seat though expected to remain, feeling “driven by a motor,” interrupting others, cannot wait his or her turn) for this subtype. It is often useful to have patients provide questionnaires to other adult observers, including those who knew them during childhood, such as parents. This collateral data can help prevent diagnosing ADHD in someone who is seeking stimulants but without symptomatology as well as aid in making the diagnosis, since evidence shows that many adults who do have ADHD often underreport symptoms.

► Treatment

A. Pharmacologic

Stimulants such as methylphenidate and amphetamine are the most effective treatment, with some of the largest effect sizes for medication treatment in psychiatric disorders. These come in both short-acting and long-acting formulations. Caution should be used to assess for potential substance abuse or diversion as well as for comorbid mood disorders that may not respond well to a stimulant prior to prescribing these medications. Atomoxetine, a nonstimulant, is a second-line agent that is FDA-approved for ADHD; it affects norepinephrine and dopamine transport and makes more of these neurotransmitters available in the brain. Bupropion has evidence of efficacy as well and may

be considered in patients in whom a stimulant is contraindicated or in those who also suffer from major depression. Desipramine, a tricyclic antidepressant, also can be effective for ADHD and may be considered in patients who have additional needs, such as a concomitant depression or neuropathic pain. Guanfacine and clonidine are two additional nonstimulant medications used primarily to treat blood pressure but with some efficacy in ADHD as well.

B. Behavioral and Other Treatments

Psychoeducation regarding ADHD should be given to all patients. Many patients are able to implement behavioral changes that either improve their functioning, such as creating calendars and organizational schemes or doing tasks in multiple timed short spurts, or can help them avoid tasks that are challenging for them in favor of complementary tasks they are more suited to (ie, selecting jobs that value more activity rather than sustained focus, or sharing in the chores at home that do not require attention to detail). Cognitive behavioral therapy has some evidence for helping residual symptoms after medication management has been optimized.

Cortese S et al. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. *Lancet Psychiatry*. 2018;5:727. [PMID: 30097390]

Nageye F et al. Beyond stimulants: a systematic review of randomised controlled trials assessing novel compounds for ADHD. *Expert Rev Neurother*. 2019;19:707. [PMID: 31167583]

comprehensive and multidisciplinary approach that includes asking about core autism spectrum disorder difficulties, early development, medical and family history, behavior, education, employment, needs assessment, risks, physical examination with potential laboratory testing, and feedback to the individual.

Treatment

No treatments for the core symptoms of autism spectrum disorder in adults have been validated. Two antipsychotics, risperidone and paliperidone, are approved for treating irritability in patients with autism spectrum disorders. These antipsychotics can help with some of the behavioral symptoms of autism but also carry a risk of metabolic side effects and extrapyramidal symptoms. There is some evidence for therapy, such as applied behavioral analysis, to address social cognitions and behaviors. Use of repetitive transcranial magnetic stimulation and vasopressin for the treatment of autism spectrum disorder are under investigation.

Howes OD et al. Autism spectrum disorder: consensus guidelines on assessment, treatment and research from the British Association for Psychopharmacology. *J Psychopharmacol*. 2018;32:3. [PMID: 29237331]

SLEEP-WAKE DISORDERS

Sleep consists of two distinct states as shown by electroencephalographic studies: (1) **REM** (rapid eye movement) sleep, also called dream sleep, D state sleep, or paradoxical sleep, and (2) **NREM** (non-REM) sleep, also called S stage sleep, which is divided into stages 1, 2, 3, and 4 and is recognizable by different electroencephalographic patterns. Stages 3 and 4 are “delta” sleep. Dreaming occurs mostly in REM and to a lesser extent in NREM sleep.

Sleep is a cyclic phenomenon, with four or five REM periods during the night accounting for about one-fourth of the total night’s sleep (1.5–2 hours). The first REM period occurs about 80–120 minutes after onset of sleep and lasts about 10 minutes. Later REM periods are longer (15–40 minutes) and occur mostly in the last several hours of sleep. Most stage 4 (deepest) sleep occurs in the first several hours.

Age-related changes in normal sleep include an unchanging percentage of REM sleep and a marked decrease in stage 3 and stage 4 sleep, with an increase in wakeful periods during the night. These normal changes, early bedtimes, and daytime naps play a role in the increased complaints of insomnia in older people. Variations in sleep patterns may be due to circumstances (eg, “jet lag”) or to idiosyncratic patterns (“night owls”) in persons who perhaps because of different “biologic rhythms” habitually go to bed late and sleep late in the morning. Creativity and rapidity of response to unfamiliar situations are impaired by loss of sleep. There are also rare individuals who have chronic difficulty in adapting to a 24-hour sleep-wake cycle (**desynchronization sleep disorder**), which can be resynchronized by altering exposure to light.

AUTISM SPECTRUM DISORDERS



ESSENTIALS OF DIAGNOSIS

- ▶ Persistent issues with social communication and interactions.
- ▶ Repetitive behaviors, interests, or activities.
- ▶ Symptoms interfere with functioning.
- ▶ May or may not have accompanying language or intellectual impairment.

Clinical Findings

Autism spectrum disorder is a neurodevelopmental disorder in which patients suffer from pervasive *difficulties with social communication* and have *repetitive, restricted interests and behaviors*. Autism spectrum disorder affects about 1% of the adult population with an estimated heritability of about 90%. Approximately 20–30% of individuals in whom autism is diagnosed also have a substance use problem as well as a higher risk of ADHD and mood or obsessive-compulsive disorders. The National Institute of Health and Care Excellence (NICE) guidelines recommend that assessment of autism spectrum disorder should be a

The three major sleep disorders are discussed below. Any persistent sleep disorder that is not attributable to another condition should be evaluated by a sleep specialist.

1. Insomnia

► Classification & Clinical Findings

Patients may complain of difficulty getting to sleep or staying asleep, intermittent wakefulness during the night, early morning awakening, or combinations of any of these. Transient episodes are usually of little significance. Stress, caffeine, physical discomfort, daytime napping, and early bedtimes are common factors.

Psychiatric disorders are often associated with persistent insomnia. Depression is usually associated with fragmented sleep, decreased total sleep time, earlier onset of REM sleep, a shift of REM activity to the first half of the night, and a loss of slow wave sleep—all of which are non-specific findings. In manic disorders, a reduced total sleep time and a decreased need for sleep are cardinal features and important early sign of impending mania. In addition to a decreased amount of sleep, manic episodes are characterized by a shortened REM latency and increased REM activity. Sleep-related panic attacks occur in the transition from stage 2 to stage 3 sleep in some patients with a longer REM latency in the sleep pattern preceding the attacks.

Abuse of alcohol may cause or be secondary to the sleep disturbance. *There is a tendency to use alcohol as a means of getting to sleep without realizing that it disrupts the normal sleep cycle.* Acute alcohol intake produces a decreased sleep latency with reduced REM sleep during the first half of the night. REM sleep is increased in the second half of the night, with an increase in total amount of slow wave sleep (stages 3 and 4). Vivid dreams and frequent awakenings are common. Chronic alcohol abuse increases stage 1 and decreases REM sleep (most medications delay or block REM sleep), with symptoms persisting for many months after the individual has stopped drinking. Acute alcohol or other sedative withdrawal causes delayed onset of sleep and REM rebound with intermittent awakening during the night.

Heavy smoking (more than a pack a day) causes difficulty falling asleep—apparently independently of the often associated increase in coffee drinking. Excess intake near bedtime of caffeine, cocaine, and other stimulants (eg, over-the-counter cold remedies) causes decreased total sleep time—mostly NREM sleep—with some increased sleep latency.

Sedative-hypnotics—specifically, the benzodiazepines, which are the most commonly prescribed medications to promote sleep—tend to increase total sleep time, decrease sleep latency, and decrease nocturnal awakening, with variable effects on NREM sleep. Nonbenzodiazepine hypnotics have similar effects on sleep as do the benzodiazepines, though some evidence shows improved slow wave sleep and less residual next-morning somnolence with nonbenzodiazepines, such as zolpidem. Withdrawal causes just the opposite effects and results in continued use of the medication for the purpose of preventing withdrawal symptoms. Antidepressants decrease REM sleep (with marked rebound on withdrawal in the form of nightmares)

and have varying effects on NREM sleep. The effect on REM sleep correlates with reports that REM sleep deprivation produces improvement in some depressions.

Persistent insomnias are also related to a wide variety of medical conditions, particularly delirium, pain, respiratory distress syndromes, uremia, asthma, thyroid disorders, and nocturia due to benign prostatic hyperplasia. Sleep apnea and restless leg movement are described below. Adequate analgesia and proper treatment of medical disorders will reduce symptoms and decrease the need for sedatives.

► Treatment

In general, there are two broad classes of treatment for insomnia, and the two may be combined: psychological (cognitive-behavioral) and pharmacologic. In situations of acute distress, such as a grief reaction, pharmacologic measures may be most appropriate. *With primary insomnia, however, initial efforts should be psychologically based.* This is particularly true in the elderly to avoid the potential adverse reactions of medications. The elderly population is at risk for complaints of insomnia because sleep becomes lighter and more easily disrupted with aging. Medical disorders that become more common with age may also predispose to insomnia.

A. Psychological

Psychological strategies should include educating the patient regarding good **sleep hygiene:** (1) Go to bed only when sleepy. (2) Use the bed and bedroom only for sleeping and sex. (3) If still awake after 20 minutes, leave the bedroom, pursue a restful activity (such as a bath or meditation), and only return when sleepy. (4) Get up at the same time every morning regardless of the amount of sleep during the night. (5) Discontinue caffeine and nicotine, at least in the evening if not completely. (6) Establish a daily exercise regimen. (7) Avoid alcohol as it may disrupt continuity of sleep. (8) Limit fluids in the evening. (9) Learn and practice relaxation techniques. (10) Establish a bedtime ritual and a routine time for going to sleep. Research suggests that *cognitive behavioral therapy for insomnia is as effective as zolpidem* with benefits sustained 1 year after treatment.

B. Pharmacologic

When the above measures are insufficient, medications may be useful. Lorazepam (0.5 mg orally nightly), temazepam (7.5–15 mg orally nightly), and the nonbenzodiazepine hypnotics zolpidem (5–10 mg orally nightly, with a limit of 5 mg indicated for women) and zaleplon (5–10 mg orally nightly) are often effective for the elderly population and can be given in larger doses—twice what is prescribed for the elderly—in younger patients. Zaleplon is often used to treat insomnia characterized by middle-of-the-night awakening with difficulty falling back to sleep. Eszopiclone (2–3 mg orally) is similar in action to zolpidem and zaleplon and has a longer duration of action. A lower dose of 1 mg is indicated in the elderly or those with hepatic impairment. It is important to note that short-acting agents like triazolam or zolpidem may lead to amnestic episodes if used on a daily ongoing basis. Longer-acting agents such as

flurazepam (half-life of more than 48 hours) may accumulate in the elderly and lead to cognitive slowing, ataxia, falls, and somnolence. In general, it is appropriate to *use medications for short courses of 1–2 weeks*. The medications described above have largely replaced barbiturates as hypnotic agents because of their greater safety in overdose and their lesser hepatic enzyme induction effects. Antihistamines such as diphenhydramine (25 mg orally nightly) or hydroxyzine (25 mg orally nightly) may also be useful for sleep, as they produce no pharmacologic dependency; their anticholinergic effects may, however, produce confusion or urinary symptoms in the elderly. Trazodone, an atypical antidepressant, is a non-habit-forming, effective sleep medication in lower than antidepressant doses (25–150 mg orally at bedtime). Priapism is a rare side effect requiring emergent treatment. Doxepin, 3–6 mg per night, is a TCA that is also effective for insomnia. Ramelteon, 8 mg orally at bedtime, is a melatonin receptor agonist that helps with sleep onset and does not appear to have abuse potential. It appears to be safe for ongoing use without the development of tolerance. Melatonin is used in doses of 3–6 mg. While melatonin is effective in reducing sleep latency, it is not usually effective in maintaining sleep. Thus, other strategies or medications are often required for sleep maintenance.

The dual orexin receptor antagonists (DORAs) class of hypnotics are approved to help initiate and maintain sleep. DORAs such as suvorexant and lemborexant may be more effective than other hypnotics for some patients. However, the role of DORAs have not been established relative to other hypnotics and DORAs are more expensive since they are not generically available. DORAs have shown a significant increase in depressive symptoms in a subset of patients, so other hypnotics may be a better choice in depressed patients. The dose of suvorexant is 10–20 mg orally given about 30 minutes before bedtime while lemborexant is typically given in dosages of 5–10 mg daily.

2. Hypersomnias (Disorders of Excessive Sleepiness)

► Classification & Clinical Findings

A. Breathing-Related Sleep Disorders

Obstructive sleep apnea is by far the most common of the breathing-related sleep disorders that include **central sleep apnea** and **sleep-related hypoventilation**. Obstructive sleep apnea hypopnea is characterized by snoring, gasping, or breathing pauses during sleep and five or more apneas or hypopneas per hour or evidence by polysomnography. (See Chapter 9.)

B. Narcolepsy Syndrome

Narcolepsy consists of a tetrad of symptoms: (1) sudden, brief (about 15 minutes) sleep attacks that may occur during any type of activity; (2) cataplexy—sudden loss of muscle tone involving specific small muscle groups or generalized muscle weakness that may cause the person to slump to the floor, unable to move, often associated with

emotional reactions and sometimes confused with seizure disorder; (3) sleep paralysis—a generalized flaccidity of muscles with full consciousness in the transition zone between sleep and waking; and (4) hypnagogic hallucinations, visual or auditory, which may precede sleep or occur during the sleep attack. The attacks are characterized by an abrupt transition into REM sleep—a necessary criterion for diagnosis. The disorder begins in early adult life, affects both sexes equally, and usually levels off in severity at about 30 years of age.

REM sleep behavior disorder, characterized by motor dyscontrol and often violent dreams during REM sleep, may be related to narcolepsy.

C. Kleine-Levin Syndrome

This syndrome, which occurs mostly in young men, is characterized by hypersomnic attacks three or four times a year lasting up to 2 days, with hyperphagia, hypersexuality, irritability, and confusion on awakening. It has often been associated with antecedent neurologic insults. It usually remits after age 40.

D. Periodic Limb Movement Disorder

Periodic lower leg movements occur only during sleep with subsequent daytime sleepiness, anxiety, depression, and cognitive impairment. **Restless leg syndrome** includes movements while awake as well.

E. Shift Work Sleep Disorder

Shift work sleep disorder occurs when there is excessive fatigue as a consequence of work occurring during the normal sleep period.

► Treatment

Narcolepsy can be managed by daily administration of a stimulant such as dextroamphetamine sulfate, 10 mg orally in the morning, with increased dosage as necessary. Modafinil and its enantiomer armodafinil are schedule IV medications FDA-approved for treating the excessive daytime fatigue of narcolepsy, sleepiness associated with obstructive sleep apnea, as well as for shift work sleep disorder. Usual dosing is 200–400 mg orally each morning for modafinil and 150–250 mg orally in the morning for armodafinil. The exact mechanism of action of modafinil and armodafinil is unknown, yet they are thought to be less of an abuse risk than stimulants that are primarily dopaminergic. Common side effects include headache and anxiety; however, modafinil appears to be generally well tolerated. Modafinil may reduce the efficacy of cyclosporine, oral contraceptives, and other medications by inducing their hepatic metabolism. Imipramine, 75–100 mg orally daily, has been effective in treatment of cataplexy but not narcolepsy.

Periodic limb movement disorder and REM sleep behavior disorder can be treated with clonazepam with variable results. There is no treatment for Kleine-Levin syndrome, although lithium can prevent recurrences in some.

Treatment of sleep apnea is discussed in Chapter 9.

3. Parasomnias (Abnormal Behaviors during Sleep)

These disorders (sleep terror, nightmares, sleepwalking, and enuresis) are fairly common in children but less so in adults.

Espie CA et al. Effect of digital cognitive behavioral therapy for insomnia on health, psychological well-being, and sleep-related quality of life: a randomized clinical trial. *JAMA Psychiatry*. 2019;76:21. [PMID: 30264137]

Krystal AD et al. The assessment and management of insomnia: an update. *World Psychiatry*. 2019;18:337. [PMID: 31496087]

DISORDERS OF AGGRESSION

Aggression and violence are symptoms rather than diseases, and most frequently they are not necessarily associated with an underlying medical condition. Clinicians are unable to predict dangerous behavior with greater than chance accuracy. Depression, schizophrenia, personality disorders, mania, paranoia, temporal lobe dysfunction, and organic mental states may be associated with acts of aggression. Impulse control disorders are characterized by physical abuse (usually of the aggressor's domestic partner or children), by pathologic intoxication, by impulsive sexual activities, and by reckless driving. Anabolic steroid usage by athletes has been associated with increased tendencies toward violent behavior.

In the United States, a significant proportion of all violent deaths are alcohol related. The ingestion of even small amounts of alcohol can result in pathologic intoxication that resembles an acute organic mental condition. Amphetamines, crack cocaine, and other stimulants are frequently associated with aggressive behavior. Phencyclidine is a drug commonly associated with violent behavior that is occasionally of a bizarre nature, partly due to lowering of the pain threshold. Domestic violence and rape are much more widespread than previously recognized. Awareness of the problem is to some degree due to increasing recognition of the rights of women and the understanding by women that they do not have to accept abuse. Acceptance of this kind of aggressive behavior inevitably leads to more, with the ultimate aggression being murder—20–50% of murders in the United States occur within the family. Police are called more for domestic disputes than all other criminal incidents combined. Children living in such family situations frequently become victims of abuse.

Features of individuals who have been subjected to long-term physical or sexual abuse are as follows: trouble expressing anger, staying angry longer, general passivity in relationships, feeling “marked for life” with an accompanying feeling of deserving to be victimized, lack of trust, and dissociation of affect from experiences. They are prone to express their psychological distress with somatization symptoms, often pain complaints. They may also have symptoms related to posttraumatic stress, as discussed above. The clinician should be suspicious about the origin of any injuries not fully explained, particularly if such incidents recur.

Treatment

A. Psychological

Management of any acutely potentially violent individual includes appropriate psychological maneuvers. Move slowly, talk slowly with clarity and reassurance, and evaluate the situation. Strive to create a setting that is minimally disturbing, and eliminate people or things threatening to the violent individual. Do not threaten and do not touch or crowd the person. Allow no weapons in the area (an increasing problem in hospital emergency departments). Proximity to a door is comforting to both the patient and the examiner. Use a negotiator who the violent person can relate to comfortably. Food and drink are helpful in defusing the situation (as are cigarettes for those who smoke). Honesty is important. Make no false promises, bolster the patient's self-esteem, and continue to engage the subject verbally until the situation is under control. This type of individual does better with strong external controls to replace the lack of inner controls over the long term. Close probationary supervision and judicially mandated restrictions can be most helpful. There should be a major effort to help the individual avoid drug use (eg, Alcoholics Anonymous). Victims of abuse are essentially treated as any victim of trauma and, not infrequently, have evidence of PTSD.

B. Pharmacologic

Pharmacologic means are often necessary whether or not psychological approaches have been successful. This is particularly true in the agitated or psychotic patient. The medications of choice in seriously violent or psychotic aggressive states are antipsychotics, given intramuscularly if necessary, every 1–2 hours until symptoms are alleviated. A number of second-generation intramuscular antipsychotics are FDA approved in the management of acute agitation, and include aripiprazole (9.75 mg/1.3 mL), ziprasidone (10 mg/0.5 mL), and olanzapine (10 mg/2 mL). The second-generation antipsychotics appear less likely than first-generation medications like haloperidol (2.5–5 mg) to cause acute extrapyramidal symptoms. However, the second-generation medications appear no more effective than first-generation medications and generally are more expensive. Benzodiazepine sedatives (eg, diazepam, 5 mg orally or intravenously every several hours) can be used for mild to moderate agitation, but are sometimes associated with a disinhibition of aggressive impulses similar to alcohol. Chronic aggressive states, particularly in patients with intellectual disabilities and brain damage (rule out causative organic conditions and medications such as anticholinergic medications in amounts sufficient to cause confusion), have been ameliorated with risperidone, 0.5–2 mg/day orally, propranolol, 40–240 mg/day orally, or pindolol, 5 mg twice daily orally (pindolol causes less bradycardia and hypotension than propranolol). Carbamazepine and valproic acid are effective in the treatment of aggression and explosive disorders, particularly when associated with known or suspected brain lesions. Lithium and SSRIs are also effective for some intermittent explosive outbursts.

Buspirone (10–45 mg/day orally) is helpful for aggression, particularly in patients with intellectual disabilities.

C. Physical

Physical management is necessary if psychological and pharmacologic means are not sufficient. It requires the active and visible presence of an adequate number of personnel (five or six) to reinforce the idea that the situation is under control despite the patient's lack of inner controls. Such an approach often precludes the need for actual physical restraint. Seclusion rooms and restraints should be used only when necessary (ambulatory restraints are an alternative), and the patient must then be observed at frequent intervals. Narrow corridors, small spaces, and crowded areas exacerbate the potential for violence in an anxious patient.

D. Other Interventions

The treatment of victims (eg, battered women) is challenging and can be complicated by a reluctance to leave the situation. Reasons for staying vary, but common themes include the fear of more violence because of leaving, the hope that the situation may ameliorate (in spite of steady worsening), and the financial aspects of the situation, which are seldom to the woman's advantage. Concerns for the children often finally compel the woman to seek help. An early step is to get the woman into a therapeutic situation that provides the support of others in similar straits. Al-Anon is frequently a valuable asset when alcohol is a factor. The group can support the victim while she gathers strength to consider alternatives without being paralyzed by fear. Many cities offer temporary emergency centers and counseling. Use the available resources, attend to any medical or psychiatric problems, and maintain a compassionate interest. Some states require clinicians to report injuries caused by abuse or suspected abuse to police authorities. See Chapter e6 for detailed discussion.

Lee AH et al. Anger and aggression treatments: a review of meta-analyses. *Curr Opin Psychol*. 2018;19:65. [PMID: 29279226]

Nash RP et al. Acute pharmacological management of behavioral and emotional dysregulation following a traumatic brain injury: a systematic review of the literature. *Psychosomatics*. 2019;60:139. [PMID: 30665668]

SUBSTANCE USE DISORDERS

The term "dependency" was previously used to describe a severe form of substance abuse and drug addiction characterized by the triad of: (1) a **psychological dependence or craving** and the behavior involved in procurement of the drug; (2) **physiologic dependence**, with withdrawal symptoms on discontinuance of the drug; and (3) **tolerance**, ie, the need to increase the dose to obtain the desired effects. The terms "dependency" and "abuse" were dropped in *DSM-5* in favor of the single term "substance use disorder," ranging from mild to severe. Many patients could have a severe and life-threatening abuse problem without ever being dependent on a drug. *Substance use disorder is a treatable, chronic medical illness*. Clinicians and health care

systems must work against bias toward people with substance use disorder. Medication-assisted treatment is available for a number of substance use disorders and is a key element in their management.

There is accumulating evidence that an *impairment syndrome* exists in many former (and current) drug users. It is believed that drug use produces damaged neurotransmitter receptor sites and that the consequent imbalance produces symptoms that may mimic other psychiatric illnesses. "**Kindling**"—repeated stimulation of the brain—renders the individual more susceptible to focal brain activity with minimal stimulation. Stimulants and depressants can produce kindling, leading to relatively spontaneous effects no longer dependent on the original stimulus. These effects may be manifested as mood swings, panic, psychosis, and occasionally overt seizure activity. The imbalance also results in frequent job changes, partner problems, and generally erratic behavior. Patients with PTSD frequently have treated themselves with a variety of drugs. Chronic abusers of a wide variety of drugs exhibit cerebral atrophy on CT scans, a finding that may relate to the above symptoms. Early recognition is important, mainly to establish realistic treatment programs that are chiefly symptom-directed.

The clinician faces three problems with substance use disorders: (1) the prescribing of substances such as sedatives, stimulants, or opioids that might produce dependency; (2) the treatment of individuals who have already misused drugs, most commonly alcohol; and (3) the detection of illicit drug use in patients presenting with psychiatric symptoms. The usefulness of **urinalysis for detection of drugs** varies markedly with different drugs and under different circumstances (pharmacokinetics is a major factor) (see also Chapter 5). Water-soluble drugs (eg, alcohol, stimulants, opioids) are eliminated in a day or so. Lipophilic substances (eg, barbiturates, tetrahydrocannabinol) appear in the urine over longer periods of time: several days in most cases, 1–2 months in chronic marijuana users. Sedative drug determinations are quite variable, amount of drug and duration of use being important determinants. False-positives can be a problem related to ingestion of some legitimate medications (eg, phenytoin for barbiturates, phenylpropanolamine for amphetamines, chlorpromazine for opioids) and some foods (eg, poppy seeds for opioids, coca leaf tea for cocaine). Manipulations can alter the legitimacy of the testing. Dilution, either *in vivo* or *in vitro*, can be detected by checking urine-specific gravity. Addition of ammonia, vinegar, or salt may invalidate the test, but odor and pH determinations are simple. Hair analysis can determine drug use over longer periods, particularly sequential drug-taking patterns. The sensitivity and reliability of such tests are considered good, and the method may be complementary to urinalysis.

O'Connor EA et al. Screening and behavioral counseling interventions to reduce unhealthy alcohol use in adolescents and adults: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2018;320:1910. [PMID: 30422198]

ALCOHOL USE DISORDER (Alcoholism)

Meshell D. Johnson, MD



ESSENTIALS OF DIAGNOSIS

- ▶ Physiologic dependence as manifested by evidence of withdrawal when intake is interrupted.
- ▶ Tolerance to the effects of alcohol.
- ▶ Evidence of alcohol-associated illnesses, such as alcoholic liver disease, cerebellar degeneration.
- ▶ Continued drinking despite strong medical and social contraindications and life disruptions.
- ▶ Impairment in social and occupational functioning.
- ▶ Depression.
- ▶ Blackouts.

General Considerations

Alcohol use disorder is a syndrome consisting of two phases: **at-risk drinking** and moderate to severe **alcohol misuse**. At-risk drinking is the repetitive use of alcohol, often to alleviate anxiety or solve other emotional problems. A moderate to severe alcohol use disorder is similar to that which occurs following the repeated use of other sedative-hypnotics and is characterized by recurrent use of alcohol despite disruption in social roles (family and work), alcohol-related legal problems, and taking safety risks by oneself and with others. The National Institute on Alcohol Abuse and Alcoholism formally defines at-risk drinking as *more than 4 drinks per day or 14 drinks per week for men or more than 3 drinks per day or 7 drinks per week for women*. A drink is defined by the Centers for Disease Control and Prevention (CDC) as 12 oz of beer, 8 oz of malt liquor, 5 oz of wine, or 1.3 oz or a "shot" of 80-proof distilled spirits of liquor. Individuals with at-risk drinking are at an increased risk for developing or are developing an alcohol use disorder. Alcohol and other drug abuse patients have a much higher prevalence of lifetime psychiatric disorders. While male-to-female ratios in alcoholic treatment agencies remain at 4:1, there is evidence that the rates are converging. Women delay seeking help, and when they do, they tend to seek it in medical or mental health settings. Adoption and twin studies indicate some genetic influence. Ethnic distinctions are important—eg, 40% of Japanese have aldehyde dehydrogenase deficiency and are more susceptible to the effects of alcohol. Depression is often present and should be evaluated carefully. The majority of suicides and intrafamily homicides involve alcohol. Alcohol is a major factor in rapes and other assaults.

There are several screening instruments that may help identify an alcohol use disorder. One of the most useful is the **Alcohol Use Disorder Identification Test (AUDIT)** (see Table 1–6).

Clinical Findings

A. Acute Intoxication

The signs of alcoholic intoxication are the same as those of overdosage with any other central nervous system depressant: drowsiness, errors of commission, psychomotor dysfunction, disinhibition, dysarthria, ataxia, and nystagmus. For a 70-kg person, an ounce of whiskey, a 4- to 6-oz glass of wine, or a 12-oz bottle of beer (roughly 15, 11, and 13 grams of alcohol, respectively) may raise the level of alcohol in the blood by 25 mg/dL. For a 50-kg person, the blood alcohol level would rise even higher (35 mg/dL) with the same consumption. Blood alcohol levels below 50 mg/dL rarely cause significant motor dysfunction (the legal limit for driving under the influence is commonly 80 mg/dL). Intoxication as manifested by ataxia, dysarthria, and nausea and vomiting indicates a blood level greater than 150 mg/dL, and lethal blood levels range from 350 mg/dL to 900 mg/dL. In severe cases, overdosage is marked by respiratory depression, stupor, seizures, shock syndrome, coma, and death. Serious overdoses are frequently due to a combination of alcohol with other sedatives.

B. Withdrawal

There is a wide spectrum of manifestations of alcohol withdrawal, ranging from anxiety, decreased cognition, and tremulousness, through increasing irritability and hyperreactivity to full-blown delirium tremens (DTs). **Alcohol withdrawal syndrome** can be categorized as mild, moderate, or severe withdrawal, withdrawal seizures, and DTs. Symptoms of mild withdrawal, including tremor, anxiety, tachycardia, nausea, vomiting, and insomnia, begin within 6 hours after the last drink, often before the blood alcohol levels drop to zero, and usually have passed by day 2. Severe or major withdrawal occurs 48–96 hours after the last drink and is usually preceded by prolonged heavy alcohol use. Symptoms include disorientation, agitation, diaphoresis, whole body tremor, vomiting, hypertension, and hallucinations (visual > tactile > auditory). Moderate withdrawal symptoms and signs fall between those of minor and major withdrawal. **Withdrawal seizures** can occur as early as 8 hours after the last drink but usually do not manifest more than 48 hours after alcohol cessation. Seizures are more prevalent in persons who have a history of withdrawal syndromes. These seizures are generalized tonic-clonic seizures, are brief in duration, and resolve spontaneously. If withdrawal is untreated, these seizures can recur in about 60% of patients. DTs will develop in approximately half of these patients. If seizures are focal, associated with trauma or fever, or have an onset more than 48 hours after the last drink, another etiology for seizures must be considered. **DT** is the most severe form of alcohol withdrawal. It is an acute organic psychosis that usually manifests 48–72 hours after the last drink, but may occur up to 7–10 days later. It is characterized by extreme mental confusion, agitation, tremor, diaphoresis, sensory hyperacuity, visual hallucinations (often of snakes, bugs, etc), and autonomic hyperactivity (tachycardia and

hypertension). Complications of DTs include (1) dehydration, (2) electrolyte disturbances (hypokalemia, hypomagnesemia), (3) arrhythmias and seizures, and (4) cardiovascular collapse and death. *The acute withdrawal syndrome is often unexpected*, occurring when the patient has been hospitalized for an unrelated problem, thus presenting as a diagnostic dilemma. Suspect alcohol withdrawal in every unexplained delirium. The mortality rate from DTs, which was upward of 35%, has steadily decreased with early diagnosis and improved treatment.

In addition to the immediate withdrawal symptoms, there is evidence of persistent longer-term ones, including sleep disturbances, anxiety, depression, excitability, fatigue, and emotional volatility. These symptoms may persist for 3–12 months, and in some cases they become chronic.

C. Alcoholic (Organic) Hallucinosis

This syndrome occurs either during heavy drinking or on withdrawal and is characterized by a paranoid psychosis without the tremulousness, confusion, and clouded sensorium seen in withdrawal syndromes. The patient appears normal except for the auditory hallucinations, which are frequently persecutory and may cause the patient to behave aggressively and in a paranoid fashion.

D. Chronic Alcoholic Brain Syndromes

These encephalopathies are characterized by increasing erratic behavior, memory and recall problems, and emotional instability—the usual signs of organic brain injury due to any cause. Wernicke-Korsakoff syndrome due to thiamine deficiency may develop with a series of episodes. **Wernicke encephalopathy** consists of the triad of confusion, ataxia, and ophthalmoplegia (typically sixth nerve palsy). Early recognition and treatment with thiamine can minimize damage. One of the possible sequelae is **Korsakoff psychosis**, characterized by both anterograde and retrograde amnesia, with confabulation early in the course. Early recognition and treatment with intravenous thiamine and B complex vitamins can minimize damage. Excessive alcohol consumption in men has been associated with faster cognitive decline compared with light to moderate alcohol consumption.

E. Laboratory Findings

Ethanol may contribute to the presence of an otherwise unexplained osmolar gap. There may also be increased serum liver biochemical tests, uric acid, and triglycerides and decreased serum potassium and magnesium. The most definitive biologic marker for chronic alcoholism is carbohydrate deficient transferrin, which can detect heavy use (60 mg/day over 7–10 days) with high specificity. Other useful tests for diagnosing alcohol use disorder are gamma-glutamyl transpeptidase (GGT) measurement (levels greater than 30 units/L are suggestive of heavy drinking) and mean corpuscular volume (MCV) (more than 95 fL in men and more than 100 fL in women). If both are elevated, a serious alcohol problem is likely. Use of other recreational drugs with alcohol skews and negates the significance of these tests.

► Differential Diagnosis

The differential diagnosis of alcoholism is essentially between **primary alcohol use disorder** (when no other major psychiatric diagnosis exists) and **secondary alcohol use disorder** (when alcohol is used as self-medication for major underlying psychiatric problems such as schizophrenia or affective disorder). The differentiation is important, since the latter group requires treatment for the specific psychiatric problem. In primary and secondary alcoholism, at-risk drinking can be distinguished from alcohol addiction by taking a careful psychiatric history and evaluating the degree to which recurrent drinking impacts the social role functioning and physical safety of the individual.

The differential diagnosis of alcohol withdrawal includes other sedative withdrawals and other causes of delirium. Acute alcoholic hallucinosis must be differentiated from other acute paranoid states such as amphetamine psychosis or paranoid schizophrenia. The form of the brain syndrome is of little help—eg, chronic brain syndromes from systemic lupus erythematosus may be associated with confabulation similar to that resulting from longstanding alcoholism.

► Complications

The medical, economic, and psychosocial problems of alcoholism are staggering. The central and peripheral nervous system complications include chronic brain syndromes, cerebellar degeneration, cardiomyopathy, and peripheral neuropathies. Direct effects on the liver include cirrhosis, esophageal varices, and eventual hepatic failure. Indirect effects include protein abnormalities, coagulation defects, hormone deficiencies, and an increased incidence of liver neoplasms.

Fetal alcohol syndrome includes one or more of the following developmental defects in the offspring of alcoholic women: (1) low birth weight and small size with failure to catch up in size or weight, (2) mental retardation, with an average IQ in the 60s, and (3) a variety of birth defects, with a large percentage of facial and cardiac abnormalities. The risk is appreciably higher with the more alcohol ingested by the mother each day.

► Treatment of At-Risk Drinking

A. Psychological

The most important consideration for the clinician is to suspect the problem early and take a nonjudgmental attitude, although this does not mean a passive one. The problem of denial must be faced, preferably with significant family members at the first meeting. This means dealing from the beginning with any *enabling behavior* of the spouse or other significant people. Enabling behavior allows the patient with an alcohol use disorder to avoid facing the consequences of his or her behavior.

There must be an emphasis on the things that can be done. This approach emphasizes the fact that the clinician cares and strikes a positive and hopeful note early in treatment. Valuable time should not be wasted trying to find

out why the patient drinks; come to grips early with the immediate problem of how to stop the drinking. Although total abstinence should be the ultimate goal, a **harm reduction model** indicates that gradual progress toward abstinence can be a useful treatment strategy.

Motivational interviewing, a model of counseling that addresses both the patient's ambivalence and motivation for change, may contribute to reduced consumption over time.

B. Social

Encourage the patient to attend **Alcoholics Anonymous** meetings and the spouse to attend **Al-Anon** meetings. Success is usually proportionate to the utilization of Alcoholics Anonymous, religious counseling, and other resources. The patient should be seen frequently for short periods.

Do not underestimate the importance of religion, particularly since the patient with alcohol use disorder is often a dependent person who needs a great deal of support. Early enlistment of the help of a concerned religious adviser can often provide the turning point for a personal conversion to sobriety.

One of the most important considerations is the patient's job—*fear of losing a job is one of the most powerful motivations for giving up alcohol*. The business community is aware of the problem; about 70% of the Fortune 500 companies offer programs to their employees to help with the problem of alcoholism. Some specific recommendations that can be offered to employers include (1) avoid placement in jobs where the alcoholic patient must be alone, eg, as a traveling buyer or sales executive, (2) use supervision but not surveillance, (3) keep competition with others to a minimum, and (4) avoid positions that require quick decision making on important matters (high-stress situations). In general, commitment to abstinence and avoidance of situations that might be conducive to drinking are most predictive of a good outcome.

C. Medical

Hospitalization is not usually necessary but may be warranted if there are concomitant medical indications. Furthermore, if patients with heavy alcohol use are hospitalized for any other reason, providers must be vigilant for signs and symptoms of alcohol withdrawal.

Because of the many medical complications of alcoholism, a complete physical examination with appropriate laboratory tests is mandatory, with special attention to the liver and nervous system. Use of sedatives as a replacement for alcohol is not desirable. Lithium is not helpful in the treatment of alcoholism.

Disulfiram (250–500 mg/day orally) has been used for many years as an aversive medication to discourage alcohol use. Disulfiram inhibits aldehyde dehydrogenase, causing toxic reactions when alcohol is consumed. The results have generally been of limited effectiveness and depend on the motivation of the individual to be compliant.

Naltrexone, an opiate antagonist, in a dosage of 50 mg orally daily, lowers relapse rates over the 3–6 months after cessation of drinking, apparently by lessening the pleasurable

effects of alcohol. One study suggests that naltrexone is most effective when given during periods of drinking in combination with therapy that supports abstinence but accepts the fact that relapses occur. Naltrexone is FDA approved for maintenance therapy. Studies indicate that it reduces alcohol craving when used as part of a comprehensive treatment program. Acamprosate (333–666 mg orally three times daily) helps reduce craving and maintain abstinence and can be continued even during periods of relapse. Both acamprosate and oral naltrexone have been associated with reduction in return to drinking.

D. Behavioral

Conditioning approaches historically have been used in some settings in the treatment of alcoholism, most commonly as a type of aversion therapy. For example, the patient is given a drink of whiskey and then a shot of apomorphine, and proceeds to vomit. In this way a strong association is built up between the drinking and vomiting. Although this kind of treatment has been successful in some cases, after appropriate informed consent, many people do not sustain the learned aversive response.

► Treatment of Hallucinosis & Withdrawal

A. Hallucinosis

Alcoholic hallucinosis, which can occur either during or on cessation of a prolonged drinking period, is not a typical withdrawal syndrome and is handled differently. Since the symptoms are primarily those of a psychosis in the presence of a clear sensorium, they are handled like any other psychosis: hospitalization (when indicated) and adequate amounts of antipsychotic medications. Haloperidol, 5 mg orally twice a day for the first day or so, usually ameliorates symptoms quickly, and the medication can be decreased and discontinued over several days as the patient improves. It then becomes necessary to deal with the chronic alcohol abuse, which has been discussed.

B. Withdrawal

The onset of withdrawal symptoms is usually 6–36 hours, and the peak intensity of symptoms is 48–72 hours after alcohol consumption is stopped. Providing adequate central nervous system depressants (eg, benzodiazepines) is important to counteract the excitability resulting from sudden cessation of alcohol intake. The choice of a specific sedative is less important than using adequate doses to bring the patient to a level of moderate sedation, and this will vary from person to person.

All patients should be evaluated for their risk of alcohol withdrawal. Mild dependency requires "drying out." For outpatients, in some instances, a short course of tapering long-acting benzodiazepines—eg, diazepam, 20 mg/day orally initially, decreasing by 5 mg daily—may be a useful adjunct. When the history or presentation suggests that patients are actively in withdrawal or at significant risk for withdrawal, they should be hospitalized. Risk factors include a recent drinking history, frequent alcohol consumption, a past history of withdrawal, seizures,

hallucinosis, or DTs, a past history of needing medication for detoxification, or a history of benzodiazepine or barbiturate use, abuse, or dependency.

For all hospitalized patients, general management includes ensuring adequate hydration, correction of electrolyte imbalances (particularly magnesium, calcium, and potassium), and administering the vitamins thiamine (100 mg intravenously daily for 3 days then orally daily), folic acid (1 mg orally daily), and a multivitamin orally daily. Thiamine should be given *prior* to any glucose-containing solutions to decrease the risk of precipitating Wernicke encephalopathy or Korsakoff syndrome. Alcohol withdrawal is treated with benzodiazepines. Continual assessment is recommended to determine the severity of withdrawal, and **symptom-driven medication regimens**, which have been shown to prevent undersedation as well as oversedation and to reduce total benzodiazepine usage over fixed-dose schedules, should be used. The severity of withdrawal will determine a patient's level of care. For those at risk for withdrawal and with mild withdrawal symptoms, admission to a medical unit is adequate. For those with moderate withdrawal, a higher acuity hospital environment is recommended. Those with severe withdrawal should be admitted to the ICU.

1. Assessing alcohol withdrawal symptom severity—The Clinical Institute Withdrawal Assessment for Alcohol, Revised (CIWA-Ar) is a validated tool that is widely used to determine severity of alcohol withdrawal. This survey assesses symptoms in 10 areas and can be administered relatively quickly (Figure 25–3). One caveat is that the patient must be able to communicate his or her symptoms to the provider. The maximum attainable score is 67. Clinical judgment should be used to determine final dosing of medications to patients who are in alcohol withdrawal because dosing will vary between patients and degrees of withdrawal.

2. Treating alcohol withdrawal symptoms based on CIWA-Ar score

A. MINIMAL WITHDRAWAL SYMPTOMS (CIWA-AR SCORE LESS THAN 8)—Patients who have a history suggestive of alcohol withdrawal risk with minimal withdrawal symptoms are suitable for withdrawal prophylaxis. The recommended benzodiazepine options include chlordiazepoxide or lorazepam orally, tapered over 3 days. The protocol calls for nursing assessment of sedation and withdrawal symptoms (CIWA-Ar) every 6 hours. If prophylactic medication is indicated, a sample tapering regimen may include lorazepam, 1 mg orally every 6 hours for 1 day, then 1 mg orally every 8 hours for 1 day, then 1 mg orally every 12 hours for 1 day, then discontinue; or chlordiazepoxide, 50 mg orally every 6 hours for 1 day, 25 mg orally every 6 hours for 2 days, then discontinue. Avoid chlordiazepoxide in the elderly or in patients with liver disease. Lorazepam is preferred in patients with liver disease. Sedation is assessed 30–60 minutes after each medication dose. The benzodiazepine dose is held for oversedation or if the respiratory rate is less than 10 breaths per minute. For CIWA-Ar score greater than 8, the provider must be notified, because this is suggestive of active withdrawal, and escalation of treatment must occur.

B. MILD WITHDRAWAL SYMPTOMS (CIWA-AR SCORE 8–15)

For patients in mild withdrawal, either chlordiazepoxide orally or lorazepam orally or intravenously can be used. Initially, chlordiazepoxide 50 mg orally or lorazepam 1 or 2 mg orally or intravenously is given hourly for 2 hours. Patients must be assessed for level of sedation and withdrawal symptoms (CIWA-Ar) every 4 hours. Dosing is adjusted as necessary to control symptoms without excessive sedation. After the first 2 hours, chlordiazepoxide or lorazepam is given every 4 hours and as needed. Typical dosing may include chlordiazepoxide 25–50 mg orally or lorazepam 0.5–1 mg orally or intravenously every 4 hours as needed. Additional doses of benzodiazepines should be given if the CIWA-Ar score remains between 8 and 15.

C. MODERATE WITHDRAWAL (CIWA-AR SCORE 16–20)

For patients in moderate withdrawal, chlordiazepoxide 100 mg orally or lorazepam 3 or 4 mg orally or intravenously is given every hour for the first 2 hours. CIWA-Ar monitoring should occur every 2 hours. Dosing is adjusted to control symptoms without excessive sedation. After initial dosing, continued treatment could include chlordiazepoxide 50 mg orally or lorazepam 1–2 mg orally or intravenously every 2 hours as needed for CIWA-Ar score between 16 and 20, and chlordiazepoxide 25 mg orally or lorazepam 0.5–1 mg orally or intravenously every 2 hours for CIWA-Ar score between 8 and 15. The maximum dose of chlordiazepoxide is 600 mg in 24 hours. Continuous pulse oximetry and cardiac monitoring should be considered. The degree of sedation should be monitored 30–60 minutes after each oral dose of medication and for 15 minutes after each parenteral dose.

D. SEVERE WITHDRAWAL (CIWA-AR SCORE GREATER THAN 20)

Patients with severe withdrawal are at risk for the development of DTs and should be transferred or admitted to the ICU. Intravenous lorazepam can be used to treat severe withdrawal. A potential treatment protocol is to administer lorazepam 1–2 mg intravenously every 15 minutes until the patient is calm and sedated but awake. Initial CIWA-Ar monitoring should occur every 30 minutes. The patient can then receive lorazepam 2 mg orally or intravenously every hour as needed when the CIWA-Ar score is between 16 and 20, and lorazepam 1–2 mg orally or intravenously every hour as needed when the CIWA-Ar score is between 8 and 15. If the patient requires more than 8 mg/h of lorazepam as an initial dose or continues to demonstrate observable agitation, tremors, tachycardia, or hypertension despite high doses of lorazepam, consider adding dexmedetomidine. Dexmedetomidine, an alpha-2-agonist, produces sedation with minimal effect on respiratory drive. It is not recommended as a sole agent for the treatment of alcohol withdrawal but as adjunctive therapy along with benzodiazepines to decrease the hyperadrenergic output in patients with severe alcohol withdrawal not controlled by benzodiazepines or in patients at risk for respiratory depression from high-dose benzodiazepine administration. The recommended dosing of dexmedetomidine is 0.2–0.7 mcg/kg/h, with lorazepam 1–2 mg intravenously every 8 hours plus lorazepam 1–2 mg intravenously every hour as needed for agitation. In limited cases of

Patient: _____ Date: _____ Time: _____ (24 hour clock, midnight = 00:00)

Pulse or heart rate, taken for 1 minute: _____ Blood pressure: _____

NAUSEA AND VOMITING — Ask "Do you feel sick to your stomach? Have you vomited?" Observation.

- 0 no nausea and no vomiting
- 1 mild nausea with no vomiting
- 2
- 3
- 4 intermittent nausea with dry heaves
- 5
- 6
- 7 constant nausea, frequent dry heaves and vomiting

TACTILE DISTURBANCES — Ask "Have you any itching, pins and needles sensations, any burning, any numbness, or do you feel bugs crawling on or under your skin?" Observation.

- 0 none
- 1 very mild itching, pins and needles, burning, or numbness
- 2 mild itching, pins and needles, burning, or numbness
- 3 moderate itching, pins and needles, burning, or numbness
- 4 moderately severe hallucinations (formications)
- 5 severe hallucinations
- 6 extremely severe hallucinations
- 7 continuous hallucinations

TREMOR — Arms extended and fingers spread apart. Observation.

- 0 no tremor
- 1 not visible, but can be felt fingertip to fingertip
- 2
- 3
- 4 moderate, with patient's arms extended
- 5
- 6
- 7 severe, even with arms not extended

AUDITORY DISTURBANCES — Ask "Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?" Observation.

- 0 not present
- 1 very mild harshness or ability to frighten
- 2 mild harshness or ability to frighten
- 3 moderate harshness or ability to frighten
- 4 moderately severe auditory hallucinations
- 5 severe hallucinations
- 6 extremely severe hallucinations
- 7 continuous hallucinations

PAROXYSMAL SWEATS — Observation.

- 0 no sweat visible
- 1 barely perceptible sweating, palms moist
- 2
- 3
- 4 beads of sweat obvious on forehead
- 5
- 6
- 7 drenching sweats

VISUAL DISTURBANCES — Ask "Does the light appear to be too bright? Is its color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?" Observation.

- 0 not present
- 1 very mild photosensitivity
- 2 mild sensitivity
- 3 moderate sensitivity
- 4 moderately severe visual hallucinations
- 5 severe hallucinations
- 6 extremely severe hallucinations
- 7 continuous hallucinations

ANXIETY — Ask "Do you feel nervous?" Observation.

- 0 no anxiety, at ease
- 1 mildly anxious
- 2
- 3
- 4 moderately anxious, or guarded, so anxiety is inferred
- 5
- 6
- 7 severely anxious, equivalent...

HEADACHE, FULLNESS IN HEAD — Ask "Does your head feel different? Does it feel like there is a band around your head?" Do not rate for dizziness or lightheadedness. Otherwise, rate severity.

- 0 not present
- 1 very mild
- 2 mild
- 3 moderate
- 4 moderately severe
- 5 severe
- 6 very severe
- 7 extremely severe

AGITATION — Observation.

- 0 normal activity
- 1 somewhat more than normal activity
- 2
- 3
- 4 moderately fidgety and restless
- 5
- 6
- 7 paces back and forth during most of the interview, or constantly thrashes about

ORIENTATION AND CLOUDING OF SENSORIUM — Ask "What is today's date?... Who am I?" Serial additions: "Please count up by 5's — 0, 5, 10..."

- 0 oriented and can do serial additions
- 1 cannot do serial additions or is uncertain about date
- 2 disoriented for date by no more than 2 calendar days
- 3 disoriented for date by more than 2 calendar days
- 4 disoriented for date and place or person

Total CIWA-Ar Score _____

Rater's Initials _____

Maximum Possible Score 67

This assessment for monitoring withdrawal symptoms requires approximately 5 minutes to administer. The maximum score is 67 (see instrument). Patients scoring less than 8 (or 10, according to some experts) do not usually need additional medication for withdrawal.

▲ **Figure 25–3.** Alcohol withdrawal assessment. (Reproduced from Sullivan JT et al. Assessment of alcohol withdrawal: The revised clinical institute withdrawal assessment for alcohol scale [CIWA-Ar]. Br J Addict. 1989;84:1353. This scale is not copyrighted and may be used freely.)

severe withdrawal requiring frequent lorazepam boluses for at least 6 hours, continuous intravenous lorazepam infusion can be considered, but the patient must be monitored extremely carefully for signs of respiratory depression. Continuous pulse oximetry and close observance of the patient's respiratory status are required. Sedation is assessed 15 minutes after each intravenous dose. If withdrawal symptoms are refractory to escalating benzodiazepine usage, despite the addition of dexmedetomidine, escalation to propofol should be considered. Patients receiving large doses of benzodiazepines often require intubation for airway protection, at which time initiation of propofol infusion for sedation, in addition to treatment of refractory alcohol withdrawal, is recommended. Phenobarbital monotherapy for alcohol withdrawal is used at some institutions, but randomized controlled trials comparing the efficacy of phenobarbital over benzodiazepines are needed to inform adoption of new treatment regimens.

In all cases, benzodiazepines should be held if the patient is too sedated or has a respiratory rate less than 10 breaths per minute. Do not bolus lorazepam in doses greater than 4 mg intravenously. Mixing benzodiazepines, eg, chlordiazepoxide orally every 8 hours with lorazepam, is not recommended. Instead, select a single agent and titrate as needed. Once a patient has been stable for 24 hours, the benzodiazepine dose can be reduced by 20% daily until withdrawal is complete.

3. Managing other withdrawal-associated conditions—

Meticulous examination for other medical problems is necessary. Alcoholic hypoglycemia can occur with low blood alcohol levels (see Chapter 27). Patients with severe alcohol use disorder commonly have liver disease with associated clotting disorders and are also prone to injury—and the combination all too frequently leads to undiagnosed subdural hematoma.

Phenytoin does *not* appear to be useful in managing alcohol withdrawal seizures per se. Sedating doses of benzodiazepines are effective in treating alcohol withdrawal seizures. Thus, other anticonvulsants are not usually needed unless there is a preexisting seizure disorder.

Chronic brain syndromes secondary to a long history of alcohol intake are not clearly responsive to thiamine and vitamin replenishment. Attention to the social and environmental care of this type of patient is paramount.

4. Initiating psychological and social measures—The psychological and behavioral treatment methods outlined under Treatment of At-Risk Drinking become the primary considerations after successful treatment of alcoholic hallucinosis or withdrawal. Psychological and social measures should be initiated in the hospital prior to discharge. This increases the possibility of continued posthospitalization treatment.

Sullivan SM et al. Comparison of phenobarbital-adjunct versus benzodiazepine-only approach for alcohol withdrawal syndrome in the ED. *Am J Emerg Med.* 2019;37:1313. [PMID: 30414743]

OTHER DRUG & SUBSTANCE USE DISORDERS

A number of recreational drugs and prescription medications may be misused. Treatment for acute intoxication is distinguished from treatment of possible use disorder.

1. Opioids

While the terms "opioids" and "narcotics" both refer to a group of drugs with actions that mimic those of morphine, the term "opioids" is used when discussing medications prescribed in a controlled manner by a clinician, and the term "narcotics" is used to connote illicit drug use. The opioid analgesics can be reversed by the opioid antagonist naloxone.

The clinical symptoms and signs of mild narcotic intoxication include changes in mood, with feelings of euphoria; drowsiness; nausea with occasional emesis; needle tracks; and miosis. The incidence of snorting and inhaling ("smoking") heroin has risen, particularly among cocaine users. Overdosage causes respiratory depression, peripheral vasodilation, pinpoint pupils, pulmonary edema, coma, and death.

Tolerance and withdrawal are major concerns when continued use of opioids occurs, although withdrawal causes only *moderate morbidity* (similar in severity to a bout of "flu"). Grades of withdrawal are categorized from 0 to 4: **grade 0** includes craving and anxiety; **grade 1**, yawning, lacrimation, rhinorrhea, and perspiration; **grade 2**, previous symptoms plus mydriasis, piloerection, anorexia, tremors, and hot and cold flashes with generalized aching; **grades 3 and 4**, increased intensity of previous symptoms and signs, with increased temperature, blood pressure, pulse, and respiratory rate and depth. In withdrawal from the most severe addiction, vomiting, diarrhea, weight loss, hemoconcentration, and spontaneous ejaculation or orgasm commonly occur.

Treatment for overdosage (or suspected overdosage) is discussed in Chapter 38.

Treatment for withdrawal begins if grade 2 signs develop. If a withdrawal program is necessary, use methadone, 10 mg orally (use parenteral administration if the patient is vomiting), and observe. If signs (piloerection, mydriasis, cardiovascular changes) persist for more than 4–6 hours, give another 10 mg; continue to administer methadone at 4- to 6-hour intervals until signs are not present (rarely greater than 40 mg of methadone in 24 hours). Divide the total amount of medication required over the first 24-hour period by 2 and give that amount every 12 hours. Each day, reduce the total 24-hour dose by 5–10 mg. Thus, a moderately addicted patient initially requiring 30–40 mg of methadone could be withdrawn over a 4- to 8-day period. Clonidine, 0.1 mg orally several times daily over a 10- to 14-day period, is both an alternative and an adjunct to methadone detoxification; it is not necessary to

Oks M et al. The safety and utility of phenobarbital use for the treatment of severe alcohol withdrawal syndrome in the medical intensive care unit. *J Intensive Care Med.* 2020;35:844. [PMID: 29925291]

Pizon AF et al. Adjunct ketamine use in the management of severe ethanol withdrawal. *Crit Care Med.* 2018;46:e768. [PMID: 29742583]

taper the dose. Clonidine is helpful in alleviating cardiovascular symptoms but does not significantly relieve anxiety, insomnia, or generalized aching. There is a protracted abstinence syndrome of metabolic, respiratory, and blood pressure changes over a period of 3–6 months. Alternative strategies for the treatment of opioid withdrawal have included rapid and ultrarapid detoxification techniques. However, data do not support the use of either method.

Treatment of opioid use disorder is key given evidence of significant morbidity and mortality, including what has been called the “opioid epidemic” in the United States. Opioid use disorder may be treated with medications and psychosocial interventions such as Narcotics Anonymous (NA). Buprenorphine, a partial agonist, is a mainstay of office-based treatment of opiate dependency. Its use requires certified training along with a special license from the Drug Enforcement Agency. Buprenorphine is a mu partial agonist and kappa antagonist. Unlike conventional opioids, buprenorphine may have a role in the treatment of major depression. Recently, a long-acting injectable form demonstrated efficacy.

Methadone maintenance programs are of some value in opioid use disorder. Under carefully controlled supervision, the person with opioid use disorder is maintained on fairly high doses of methadone (40–120 mg daily) that satisfy craving and block the effects of heroin to a great degree.

Opioid antagonists (eg, naltrexone) can also be used successfully for treatment of the patient who has been free of opioids for 7–10 days. Naltrexone blocks the narcotic “high” of heroin when 50 mg is given orally every 24 hours initially for several days and then 100 mg is given every 48–72 hours. A monthly injectable form of naltrexone is available and may enhance compliance. Liver disorders are a major contraindication.

- Bohnert ASB et al. Understanding links among opioid use, overdose, and suicide. *N Engl J Med.* 2019;380:71. [PMID: 30601750]
- Haight BR et al; RB-US-13-0001 Study Investigators. Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2019;393:778. [PMID: 30792007]
- Jones CM et al. Naloxone co-prescribing to patients receiving prescription opioids in the Medicare Part D program, United States, 2016–2017. *JAMA.* 2019;322:462. [PMID: 31386124]
- Leshner AI et al. Medication-based treatment to address opioid use disorder. *JAMA.* 2019;321:2071. [PMID: 31046072]
- National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Sciences Policy; Committee on Medication-Assisted Treatment for Opioid Use Disorder; Mancher M et al (editors). *Medications for Opioid Use Disorder Save Lives.* Washington (DC): National Academies Press (US), 2019. [PMID: 30896911]

2. Sedatives (Anxiolytics)

See Anxiety Disorders, this chapter.

3. Psychedelics

Substance use disorder with psychedelics is not common. All of the common psychedelics (LSD, mescaline, psilocybin, dimethyltryptamine, and other derivatives of phenylalanine

and tryptophan) can produce similar behavioral and physiologic effects. An initial feeling of tension is followed by emotional release such as crying or laughing (1–2 hours). Later and at higher doses, perceptual distortions occur, with visual illusions and hallucinations, and occasionally there is fear of ego disintegration (2–3 hours). Major changes in time sense and mood lability then occur (3–4 hours). A feeling of detachment and a sense of destiny and control occur (4–6 hours). Of course, reactions vary among individuals, and some of the drugs produce markedly different time frames. Occasionally, the acute episode is terrifying (a “bad trip”), which may include panic, depression, confusion, or psychotic symptoms. Preexisting emotional problems, the attitude of the user, and the setting where the drug is used affect the experience.

Treatment of the acute episode primarily involves protection of the individual from erratic behavior that may lead to injury or death. A structured environment is usually sufficient until the drug is metabolized. In severe cases, antipsychotic medications with minimal side effects (eg, haloperidol, 5 mg intramuscularly) may be given every several hours until the individual has regained control. In cases where “flashbacks” occur (mental imagery from a “bad trip” that is later triggered by mild stimuli such as marijuana, alcohol, or psychic trauma), a short course of an antipsychotic medication—eg, olanzapine, 5–10 mg/day orally, or risperidone, 2 mg/day orally, initially, and up to 20 mg/day and 6 mg/day, respectively—is usually sufficient. Lorazepam or clonazepam, 1–2 mg orally every 2 hours as needed for acute agitation, may be a useful adjunct. An occasional patient may have “flashbacks” for much longer periods and may require small doses of antipsychotic medications over the longer term.

4. Phencyclidine

Phencyclidine (PCP, angel dust, peace pill, hog) is simple to produce and mimics to some degree the traditional psychedelic drugs. PCP is a common deceptive substitute for LSD, tetrahydrocannabinol, and mescaline. It is available in crystals, capsules, and tablets to be inhaled, injected, swallowed, or smoked (it is commonly sprinkled on marijuana).

Treatment for acute intoxication is discussed in Chapter 38.

5. Marijuana

Cannabis sativa, a hemp plant, is the source of marijuana. The drug is usually inhaled by smoking but vaporizing is popular. There is a clinically distinct syndrome associated with “vaping” THC—**vaping-associated lung injury**—that may result in devastating pulmonary effects and a pathologically distinct pathophysiology. Effects occur in 10–20 minutes and last 2–3 hours. “Joints” of good quality contain about 500 mg of marijuana (which contains approximately 5–15 mg of tetrahydrocannabinol with a half-life of 7 days).

With moderate dosage, recreational marijuana (higher in the THC versus CBD component) produces two phases: mild euphoria followed by sleepiness. In the acute state, the user has an altered time perception, less inhibited

emotions, psychomotor problems, impaired immediate memory, and conjunctival injection. High doses produce transient psychotomimetic effects. No specific treatment is necessary except in the case of the occasional “bad trip,” in which case the person is treated in the same way as for psychedelic usage. Marijuana frequently aggravates existing mental illness and adversely affects motor performance.

Studies of long-term effects have conclusively shown abnormalities in the pulmonary tree. Laryngitis and rhinitis are related to prolonged use, along with chronic obstructive pulmonary disease. Electrocardiographic abnormalities are common, but no chronic cardiac disease has been linked to marijuana use. Long-term usage has resulted in depression of plasma testosterone levels and reduced sperm counts. Abnormal menstruation and failure to ovulate have occurred in some women. Cognitive impairments are common. Health care utilization for a variety of health problems is increased in long-term marijuana smokers. Sudden withdrawal produces insomnia, nausea, myalgia, and irritability. Psychological effects of long-term marijuana usage are still unclear. Urine testing is reliable if samples are carefully collected and tested. Detection periods span 4–6 days in short-term users and 20–50 days in long-term users. At the beginning of 2021, in the United States, marijuana is legal for medical use, recreational use, or both, or decriminalized, in all but six states.

6. Stimulants: Amphetamines & Cocaine

Stimulant misuse is quite common, either alone or in combination with abuse of other drugs. The stimulants include illicit drugs such as methamphetamine (“speed”—one variant is a smokable form called “ice,” which gives an intense and fairly long-lasting high—and methylphenidate and dextroamphetamine, which are under prescription control. Moderate usage of any of the stimulants produces hyperactivity, a sense of enhanced physical and mental capacity, and sympathomimetic effects. The clinical picture of acute stimulant intoxication includes sweating, tachycardia, elevated blood pressure, mydriasis, hyperactivity, and an acute brain syndrome with confusion and disorientation. Tolerance develops quickly, and, as the dosage is increased, hypervigilance, paranoid ideation (with delusions of parasitosis), stereotypy, bruxism, tactile hallucinations of insect infestation, and full-blown psychoses occur, often with persecutory ideation and aggressive responses. Stimulant withdrawal is characterized by depression with symptoms of hyperphagia and hypersomnia.

People who have used stimulants chronically (eg, anorexigenics) occasionally become sensitized (“kindling”) to future use of stimulants. In these individuals, even small amounts of mild stimulants such as caffeine can cause symptoms of paranoia and auditory hallucinations.

Cocaine is a stimulant. It is a product of the coca plant. The derivatives include seeds, leaves, coca paste, cocaine hydrochloride, and the free base of cocaine. Cocaine hydrochloride is the salt and the most commonly used form. Freebase, a purer (and stronger) derivative called “crack,” is prepared by simple extraction from cocaine hydrochloride.

There are various modes of use. Coca leaf chewing involves toasting the leaves and chewing with alkaline material (eg, the ash of other burned leaves) to enhance buccal absorption. One achieves a mild high, with onset in 5–10 minutes and lasting for about an hour. Intranasal use is simply snorting cocaine through a straw. Absorption is slowed somewhat by vasoconstriction (which may eventually cause tissue necrosis and septal perforation); the onset of action is in 2–3 minutes, with a moderate high (euphoria, excitement, increased energy) lasting about 30 minutes. The purity of the cocaine is a major determinant of the high. Intravenous use of cocaine hydrochloride or “freebase” is effective in 30 seconds and produces a short-lasting, fairly intense high of about 15 minutes’ duration. The combined use of cocaine and ethanol results in the metabolic production of cocaethylene by the liver. This substance produces more intense and long-lasting cocaine-like effects. Smoking freebase (volatilized cocaine because of the lower boiling point) acts in seconds and results in an intense high lasting several minutes. The intensity of the reaction is related to the marked lipid solubility of the freebase form and produces by far the most severe medical and psychiatric symptoms.

Cardiovascular collapse, arrhythmias, myocardial infarction, and transient ischemic attacks have been reported. Seizures, strokes, migraine symptoms, hyperthermia, and lung damage may occur, and there are several obstetric complications, including spontaneous abortion, abruptio placentae, teratogenic effects, delayed fetal growth, and prematurity. Cocaine can cause anxiety, mood swings, and delirium, and chronic use can cause the same problems as other stimulants.

Clinicians should be alert to cocaine use in patients presenting with unexplained nasal bleeding or septal perforations, headaches, fatigue, insomnia, anxiety, depression, and chronic hoarseness. Sudden withdrawal of the drug is not life-threatening but usually produces craving, sleep disturbances, hyperphagia, lassitude, and severe depression (sometimes with suicidal ideation) lasting days to weeks.

Treatment for acute intoxication is imprecise and difficult. Since the high is related to blockage of dopamine reuptake, the dopamine agonist bromocriptine, 1.5 mg orally three times a day, alleviates some of the symptoms of craving associated with acute cocaine withdrawal. Treatment of psychosis is the same as that of any psychosis: antipsychotic medications in dosages sufficient to alleviate the symptoms. Any medical symptoms (eg, hyperthermia, seizures, hypertension) are treated specifically. These approaches should be used in conjunction with a structured program for use disorder, most often based on the Alcoholics Anonymous model. Hospitalization may be required if self-harm or violence toward others is a perceived threat (usually indicated by paranoid delusions).

7. Caffeine

Caffeine, along with nicotine and alcohol, is one of the most commonly used drugs worldwide although a caffeine use disorder is not described. Low to moderate doses (30–200 mg/day) tend to improve some aspects of

performance (eg, vigilance). The approximate content of caffeine in a (180-mL) cup of beverage is as follows: brewed coffee, 80–140 mg; instant coffee, 60–100 mg; decaffeinated coffee, 1–6 mg; black leaf tea, 30–80 mg; tea bags, 25–75 mg; instant tea, 30–60 mg; cocoa, 10–50 mg; and 12-oz cola drinks, 30–65 mg. A 2-oz chocolate candy bar has about 20 mg. Some herbal teas (eg, “morning thunder”) contain caffeine. Caffeine-containing analgesics usually contain approximately 30 mg per unit. Symptoms of caffeineism (usually associated with ingestion of over 500 mg/day) include anxiety, agitation, restlessness, insomnia, a feeling of being “wired,” and somatic symptoms referable to the heart and gastrointestinal tract. It is common for a case of caffeineism to present as an anxiety disorder. It is also common for caffeine and other stimulants to precipitate severe symptoms in compensated schizophrenic and manic-depressive patients. Chronically depressed patients often use caffeine drinks as self-medication. This diagnostic clue may help distinguish some major affective disorders. Discontinuation of caffeine (greater than 250 mg/day) can produce withdrawal symptoms, such as headaches, irritability, lethargy, and occasional nausea.

8. Miscellaneous Drugs & Solvents

The principal over-the-counter drugs of concern are an assortment of antihistaminic agents, frequently in combination with a mild analgesic promoted as cold remedies.

Antihistamines usually produce some central nervous system depression—thus their use as over-the-counter sedatives. Practically all of the so-called sleep aids are antihistamines. The mixture of antihistamines with alcohol usually exacerbates the central nervous system effects. Scopolamine and bromides generally have been removed from over-the-counter products.

The abuse of laxatives sometimes can lead to electrolyte disturbances that may contribute to the manifestations of a delirium. The greatest use of laxatives tends to be in the elderly and in those with eating disorders, both of whom are the most vulnerable to physiologic changes.

Anabolic steroids are abused by people who wish to increase muscle mass for cosmetic reasons or for greater strength. In addition to the medical problems, the practice is sometimes associated with significant mood swings, aggressiveness, and paranoid delusions. Alcohol and stimulant use are higher in these individuals. Withdrawal symptoms of steroid dependency include fatigue, depressed mood, restlessness, and insomnia.

Amyl nitrite is used as an “orgasm expander.” The changes in time perception, “rush,” and mild euphoria caused by the drug prompted its nonmedical use. Subjective effects last from 5 seconds to 15 minutes. Tolerance develops readily, but there are no known withdrawal symptoms. Abstinence for several days reestablishes the previous level of responsiveness. Long-term effects may include damage to the immune system and respiratory difficulties.

Sniffing of solvents and inhaling of gases (including aerosols) produce a form of inebriation similar to that of the volatile anesthetics. Agents include gasoline, toluene, petroleum ether, lighter fluids, cleaning fluids, paint

thinners, and solvents that are present in many household products (eg, nail polish). Typical intoxication states include euphoria, slurred speech, hallucinations, and confusion, and with high doses, acute manifestations are unconsciousness and cardiorespiratory depression or failure; chronic exposure produces a variety of symptoms related to the liver, kidney, bone marrow, or heart. Lead encephalopathy can be associated with sniffing leaded gasoline. In addition, studies of workers chronically exposed to jet fuel showed significant increases in neurotoxic symptoms, including fatigue, anxiety, mood changes, memory difficulties, and somatic complaints. These same problems have been noted in long-term solvent abuse.

The so-called designer drugs are synthetic substitutes for commonly used recreational drugs. Common designer drugs include methyl analogs of fentanyl used as heroin substitutes. MDMA is also a designer drug not only with high abuse potential and purported neurotoxicity but also with therapeutic uses that are being explored. Often not detected by standard toxicology screens, these substances can present a vexing problem for clinicians faced with symptoms from a totally unknown cause.

Manhapra A et al. Pain and addiction: an integrative therapeutic approach. *Med Clin North Am.* 2018;102:745. [PMID: 29933827]

Volkow ND et al. Prevention and treatment of opioid misuse and addiction: a review. *JAMA Psychiatry.* 2019;76:208. [PMID: 30516809]

Wolf C et al. Management of alcohol withdrawal in the emergency department: current perspectives. *Open Access Emerg Med.* 2020;12:53. [PMID: 32256131]

NEUROCOGNITIVE DISORDERS

ESSENTIALS OF DIAGNOSIS

- ▶ Transient or permanent brain dysfunction with alterations in awareness or attention.
- ▶ Cognitive impairment to varying degrees.
- ▶ Impaired recall and recent memory, inability to focus attention and problems in perceptual processing, often with psychotic ideation.
- ▶ Random psychomotor activity such as stereotypy.
- ▶ Emotional disorders frequently present: depression, anxiety, irritability.
- ▶ Behavioral disturbances: impulse control, sexual acting-out, attention deficits, aggression, and exhibitionism.

General Considerations

The organic problem may be a primary brain disorder or a secondary manifestation of some general disorder. All of the cognitive disorders show *some degree of impaired thinking* depending on the site of involvement, the rate of onset and

progression, and the duration of the underlying brain lesion. Emotional disturbances (eg, depression) are often present as significant comorbidities. The behavioral disturbances tend to be more common with chronicity, more directly related to the underlying personality or central nervous system vulnerability to drug side effects, and not necessarily correlated with cognitive dysfunction.

The causes of cognitive disorders are listed in Table 25–11.

► Clinical Findings

The many manifestations include problems with orientation, short or fluctuating attention span, loss of recent memory and recall, impaired judgment, emotional lability, lack of initiative, impaired impulse control, inability to reason through problems, depression (worse in mild to moderate types), confabulation (not limited to alcohol organic brain syndrome), constriction of intellectual functions, visual and auditory hallucinations, and delusions. Physical findings will vary according to the cause. The electroencephalogram usually shows generalized slowing in delirium.

A. Delirium

Delirium (**acute confusional state**) is a transient global disorder of attention, with clouding of consciousness,

usually a result of systemic problems (eg, medications, hypoxemia). See Chapters 4 and 24. Onset is usually rapid. The mental status fluctuates (impairment is usually least in the morning), with varying inability to concentrate, maintain attention, and sustain purposeful behavior. There is a marked deficit of short-term memory and recall. Anxiety and irritability are common. Orientation problems follow the inability to retain information. Perceptual disturbances (often visual hallucinations) and psychomotor restlessness with insomnia are common. “**Sundowning**

B. Dementia

Dementia is characterized by chronicity and deterioration of selective mental functions. See Chapters 4 and 24.

In all types of dementia, loss of impulse control (sexual and language) is common. **Pseudodementia** is a term previously applied to depressed patients who appear to be demented. These patients are often identifiable by their tendency to complain about memory problems vociferously rather than try to cover them up. They usually say they cannot complete cognitive tasks but with encouragement can

Table 25–11. Etiology of delirium and other cognitive disorders (listed in alphabetical order).

Disorder	Possible Causes
Cardiovascular disorders	Myocardial infarctions, cardiac arrhythmias, cerebrovascular spasms, hypertensive encephalopathy, hemorrhages, embolisms, and occlusions indirectly cause decreased cognitive function.
Collagen-vascular and immunologic disorders	Autoimmune disorders, including systemic lupus erythematosus, Sjögren syndrome, and AIDS.
Degenerative diseases	Alzheimer disease, Pick disease, multiple sclerosis, parkinsonism, Huntington chorea, normal pressure hydrocephalus.
Endocrine disorders	Thyrotoxicosis, hypothyroidism, adrenocortical dysfunction (including Addison disease and Cushing syndrome), pheochromocytoma, insulinoma, hypoglycemia, hyperparathyroidism, hypoparathyroidism, panhypopituitarism, diabetic ketoacidosis.
Infections	Septicemia; meningitis and encephalitis due to bacterial, viral, fungal, parasitic, or tuberculous organisms or to central nervous system syphilis; acute and chronic infections due to the entire range of microbiologic pathogens.
Intoxication	Alcohol, sedatives, bromides, analgesics (eg, pentazocine), psychedelic drugs, stimulants, and household solvents.
Long-term effects of alcohol	Wernicke-Korsakoff syndrome.
Medication withdrawal	Withdrawal from alcohol, sedative-hypnotics, corticosteroids.
Medications	Anticholinergic medications, antidepressants, H ₂ -blocking agents, digoxin, salicylates (long-term use), and a wide variety of other over-the-counter and prescribed medications.
Metabolic disturbances	Fluid and electrolyte disturbances (especially hyponatremia, hypomagnesemia, and hypercalcemia), acid-base disorders, hepatic disease (hepatic encephalopathy), kidney failure, porphyria.
Neoplasms	Primary or metastatic lesions of the central nervous system, cancer-induced hypercalcemia.
Nutritional deficiencies	Deficiency of vitamin B ₁ (beriberi), vitamin B ₁₂ (pernicious anemia), folic acid, nicotinic acid (pellagra); protein-calorie malnutrition.
Respiratory disorders	Hypoxia, hypercapnia.
Seizure disorders	Ictal, interictal, and postictal dysfunction.
Trauma	Subdural hematoma, subarachnoid hemorrhage, intracerebral bleeding, concussion syndrome.

often do so. They can be considered to have depression-induced reversible dementia that improves when the depression resolves. In many geriatric patients, however, the depression appears to be an insult that often unmasks a progressive dementia.

C. Amnestic Syndrome

This is a memory disturbance without delirium or dementia. It is usually associated with thiamine deficiency and chronic alcohol use (eg, Korsakoff syndrome). There is an impairment in the ability to learn new information or recall previously learned information.

D. Substance-Induced Hallucinosis

This condition is characterized by persistent or recurrent hallucinations (usually auditory) without the other symptoms usually found in delirium or dementia. Alcohol or hallucinogens are often the cause. There does not have to be any other mental disorder, and there may be complete spontaneous resolution.

► Treatment

See Chapters 4 and 24 for detailed discussion.

- Atri A. Current and future treatments in Alzheimer's disease. *Semin Neurol*. 2019;39:227. [PMID: 30925615]
Blanco-Silvente L et al. Discontinuation, efficacy, and safety of cholinesterase inhibitors for Alzheimer's disease: a meta-analysis and meta-regression of 43 randomized clinical trials enrolling 16 106 patients. *Int J Neuropsychopharmacol*. 2017;20:519. [PMID: 28201726]
Devlin JW et al. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. *Crit Care Med*. 2018;46:e825. [PMID: 30113379]

▼ PSYCHIATRIC PROBLEMS ASSOCIATED WITH HOSPITALIZATION & ILLNESS

► Diagnostic Categories

A. Acute Problems

1. Delirium with psychotic features secondary to the medical or surgical problem, or compounded by effect of treatment.
2. Acute anxiety, often related to ignorance and fear of the immediate problem as well as uncertainty about the future.
3. Anxiety as an intrinsic aspect of the medical problem (eg, hyperthyroidism).
4. Denial of illness, which may present during acute or intermediate phases of illness.

B. Intermediate Problems

1. Depression as a function of the illness or acceptance of the illness, often associated with realistic or fantasized hopelessness about the future.

2. Behavioral problems, often related to denial of illness and, in extreme cases, causing the patient to leave the hospital against medical advice.

C. Recuperative Problems

1. Decreasing cooperation as the patient sees that improvement and compliance are not compelled.
2. Readjustment problems with family, job, and society.

► General Considerations

A. Acute Problems

1. "Intensive care unit psychosis"—The ICU environment may contribute to the etiology of delirium. Critical care unit factors include sleep deprivation, increased arousal, mechanical ventilation, and social isolation. Other causes include those common to delirium and require vigorous investigation (see Delirium).

2. Presurgical and postsurgical anxiety states—Anxiety before or after surgery is common and commonly ignored. **Presurgical anxiety** is very common and is principally a fear of death (many surgical patients make out their wills). Patients may be fearful of anesthesia (improved by the preoperative anesthesia interview), the mysterious operating room, and the disease processes that might be uncovered by the surgeon. Such fears frequently cause people to delay examinations that might result in earlier surgery and a greater chance of cure.

The opposite of this is **surgery proneness**, the quest for surgery to escape from overwhelming life stresses. Some polysurgery patients may be classified as having factitious disorders. Dynamic motivations include the need to get medical care as a way of getting dependency needs met, the desire to outwit authority figures, unconscious guilt, or a masochistic need to suffer. Frequent surgery may also be related to a somatic symptom disorder, particularly body dysmorphic disorder (an obsession that a body part is disfigured). More apparent reasons may include an attempt to get relief from pain and a lifestyle that has become almost exclusively medically oriented, with all of the risks entailed in such an endeavor.

Postsurgical anxiety states are usually related to pain, procedures, and loss of body image. Acute pain problems are quite different from chronic pain disorders (see Chronic Pain Disorders, this chapter); the former are readily handled with adequate analgesic medication (see Chapter 5). Alterations in body image, as with amputations, ostomies, and mastectomies, often raise concerns about relationships with others.

3. Iatrogenic problems—These usually pertain to medications, complications of diagnostic and treatment procedures, and impersonal and unsympathetic staff behavior. Polypharmacy is often a factor. Patients with unsolved diagnostic problems are at higher risk. They are desirous of relief, and the quest engenders more diagnostic procedures with a higher incidence of complications. The upset patient and family may be very demanding. Excessive demands usually result from anxiety. Such behavior is best handled with calm and measured responses.

B. Intermediate Problems

1. Prolonged hospitalization—Prolonged hospitalization presents unique problems in certain hospital services, eg, burn units or orthopedic services. The acute problems of the severely burned patient are discussed in Chapter 37. The problems often are behavioral difficulties related to length of hospitalization and necessary procedures. For example, in burn units, pain is a major problem in addition to anxiety about procedures. Disputes with staff are common and often concern pain medication or ward privileges. Some patients regress to infantile behavior and dependency. Staff members must agree about their approach to the patient in order to ensure the smooth functioning of the unit.

Denial of illness may present in some patients. Intervention by an authority figure (eg, immediate work supervisor) may help the patient accept treatment and eventually abandon the coping mechanism of denial.

2. Depression—Mood disorders ranging from mild adjustment disorder to major depressive disorder frequently occur during prolonged hospitalizations. A key to the diagnosis of depression in the medical setting is the individual's loss of self-esteem; they often think of themselves as worthless and are guilt ridden. Therapeutic medications (eg, corticosteroids) may be a factor. Depression can contribute to irritability and overt anger. Severe depression can lead to anorexia, which further complicates healing and metabolic balance. It is during this period that the issue of disfigurement arises—relief at survival gives way to concern about future function and appearance.

C. Recuperative Problems

1. Anxiety—Anxiety about return to the posthospital environment can cause regression to a dependent position. Complications increase, and staff forbearance again is tested. Anxiety occurring at this stage usually is handled more easily than previous behavior problems.

2. Posthospital adjustment—Adjustment difficulties after discharge are related to the severity of the deficits and the use of outpatient facilities (eg, physical therapy, rehabilitation programs, psychiatric outpatient treatment). Some patients may experience posttraumatic stress symptoms (eg, from traumatic injuries or even from necessary medical treatments). Lack of appropriate follow-up can contribute to depression in the patient, who may feel that he or she is making poor progress and may have thoughts of "giving up." Reintegration into work, educational, and social endeavors may be slow.

hospitalization often brings out these more primitive defense mechanisms than the patient displays in daily life.

► Complications

Prolongation of hospitalization causes increased expense, deterioration of patient-staff relationships, and increased probabilities of iatrogenic and legal problems. The possibility of increasing posthospital treatment problems is enhanced.

► Treatment

A. Medical

The most important consideration by far is to *have one clinician in charge*, a clinician whom the patient trusts and who is able to oversee multiple treatment approaches (see Somatic Symptom Disorders, above). In acute problems, attention must be paid to metabolic imbalance, alcohol withdrawal, and previous drug use—prescribed, recreational, or over-the-counter. Adequate sleep and analgesia are important in enhancing a patient's coping abilities.

Many clinicians are attuned to the early detection of the surgery-prone patient. Plastic and orthopedic surgeons are at particular risk. Appropriate consultations may help detect some problems and mitigate future ones.

Postsurgical anxiety states can be alleviated by personal attention from the surgeon. Anxiety is not so effectively lessened by ancillary medical personnel, whom the patient perceives as lesser authorities, until after the clinician has reassured the patient. "Patient-controlled analgesia" can improve pain control, decrease anxiety, and minimize side effects.

Depression should be recognized early. If moderate to severe, antidepressant medications (see Antidepressant Medications, above) may be prescribed. High levels of anxiety can be lowered with judicious use of anxiolytic agents. Unnecessary medications tend to reinforce the patient's impression that there must be a serious illness or medication would not be required.

B. Psychological

Prepare the patient and family for what is to come. This includes the types of units where the patient will be quarantined, the procedures that will be performed, and any disfigurements that will result from surgery. Repetition improves understanding. The nursing staff can be helpful, since patients frequently confide a lack of understanding to a nurse but are reluctant to do so to the physician.

Denial of illness is frequently a block to acceptance of treatment. This too should be handled with family members present (to help the patient face the reality of the situation) in a series of short interviews (for reinforcement). Dependency problems resulting from long hospitalization are best handled by focusing on the changes to come as the patient makes the transition to the outside world. Key figures are teachers, vocational counselors, and physical therapists. Challenges should be realistic and practical and handled in small steps.

► Clinical Findings

The symptoms that occur in these patients are similar to those discussed in previous sections of this chapter, eg, delirium, stress and adjustment disorders, anxiety, and depression. Behavior problems may include lack of cooperation, increased complaints, demands for medication, sexual approaches to nurses, threats to leave the hospital, and actual signing out against medical recommendations. The stress of

Depression is usually related to the loss of familiar hospital supports, and the outpatient therapists and counselors help to lessen the impact of the loss. Some of the impact can be alleviated by anticipating, with the patient and family, the signal features of the common depression to help prevent the patient from assuming a permanent sick role.

Suicide is always a concern when a patient is faced with despair. An honest, compassionate, and supportive approach will help sustain the patient during this trying period.

C. Behavioral

Prior desensitization can significantly allay anxiety about medical procedures. A “dry run” can be done to reinforce the oral description. Cooperation during acute problem periods can be enhanced by the use of appropriate reinforcers such as a favorite nurse or helpful family member. People who are positive reinforcers are even more helpful during the intermediate phases when the patient becomes resistant to the seemingly endless procedures (eg, debridement of burned areas).

Specific situations (eg, psychological dependency on the respirator) can be corrected by weaning with appropriate reinforcers (eg, watching a favorite movie on a media player or laptop when disconnected from the ventilator). Behavioral approaches should be used in a positive and optimistic way for maximal reinforcement.

Relaxation techniques, hypnosis, and attentional distraction can be used to block side effects of a necessary treatment (eg, nausea in cancer chemotherapy).

D. Social

A change in environment requires adaptation. Because of the illness, admission and hospitalization may be more easily handled than discharge. A predischarge evaluation must be made to determine whether the family will be able to cope with the physical or mental changes in the patient. Working with the family while the patient is in the acute stage may presage a successful transition later on.

Development of a new social life can be facilitated by various self-help organizations (eg, the stoma club). Sharing problems with others in similar circumstances eases the return to a social life, which may be quite different from that prior to the illness.

► Prognosis

The prognosis is good in all patients who have reversible medical and surgical conditions. It is guarded when there is serious functional loss that impairs vocational, educational, or societal possibilities—especially in the case of progressive and ultimately life-threatening illness.

Hshieh TT et al. Delirium in the elderly. Psychiatr Clin North Am. 2018 Mar;41(1):1-17. [PMID: 29412839]

26

Endocrine Disorders

Paul A. Fitzgerald, MD

DISEASES OF THE HYPOTHALAMUS & PITUITARY GLAND

ANTERIOR HYPOPITUITARISM



ESSENTIALS OF DIAGNOSIS

- ▶ Adrenocorticotropic hormone (ACTH) deficiency: low adrenal secretion of cortisol and epinephrine; normal aldosterone secretion.
- ▶ Growth hormone (GH) deficiency: short stature in children; asthenia, obesity, and increased cardiovascular risk in adults.
- ▶ Prolactin (PRL) deficiency: postpartum lactation failure.
- ▶ Thyroid-stimulating hormone (TSH) deficiency: secondary hypothyroidism.
- ▶ Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) deficiency: hypogonadism and infertility in men and women.

General Considerations

The anterior pituitary hormones are GH, PRL, ACTH, TSH, LH, and FSH. The posterior pituitary hormones are oxytocin and arginine vasopressin (AVP), also known as antidiuretic hormone (ADH).

1. Hypopituitarism with mass lesions—

A. PITUITARY NEUROENDOCRINE TUMORS—These tumors, also known as pituitary adenomas, can cause anterior hypopituitarism, particularly when they are large macroadenomas (1 cm or larger). Nonfunctioning pituitary neuroendocrine tumors are more likely than functioning pituitary adenomas to grow large enough to cause anterior hypopituitarism; they rarely cause diabetes insipidus. Other mass lesions include craniopharyngioma, plasmacytoma, germ cell tumors, glioma, lymphomas, cysts (Rathke cleft, dermoid, epidermoid, arachnoid), meningioma, and hemangiopericytoma. Vascular lesions include

pituitary tumor apoplexy, acute Sheehan syndrome, cavernous sinus aneurysm, and subarachnoid hemorrhage. Inflammatory/infiltrative lesions include granulomatosis with polyangiitis, xanthomatosis, giant cell granuloma, Langerhans cell histiocytosis, sarcoidosis, syphilis, hypophysitis, and tuberculosis. Infectious lesions can be bacterial, fungal, or parasitic.

B. PITUITARY METASTASES—These lesions are usually from breast cancer (45%), particularly when HER2 positive; about 50% present over 10 years after the primary tumor. Lung cancer accounts for about 21% of pituitary metastases that typically present either before or within 1 year of the primary cancer. Pituitary metastases often present with visual loss or ophthalmoplegia, ACTH deficiency (71%), TSH deficiency (65%), diabetes insipidus (26%), or gonadotropin deficiency (88%).

Lymphocytic hypophysitis is an autoimmune disorder affecting the pituitary gland. It is characterized by infiltration of the infundibulum and pituitary by lymphocytes, macrophages, and plasma cells. Spontaneous lymphocytic hypophysitis is more common in women (71%) and most frequently presents during pregnancy or postpartum. The condition is often associated with other autoimmune conditions, such as systemic lupus erythematosus (SLE) or autoimmune (Hashimoto) thyroiditis. Immune checkpoint inhibitor hypophysitis can be caused by several immunity-enhancing drugs, particularly the anti-CTLA-4 agents ipilimumab and tremelimumab (14%), as well as with the anti-PD-1 agents pembrolizumab and nivolumab (0.5%). Symptoms of hypophysitis develop a median of 9 weeks after beginning ipilimumab and a median of 26 weeks after commencing an anti-PD-1 agent.

Pituitary stalk thickening is caused most frequently by autoimmune hypophysitis, metastases, neurosarcoidosis, or a congenital ectopic posterior pituitary, but in many patients, the cause is never clinically apparent. Pituitary stalk damage frequently causes central diabetes insipidus and one or more anterior pituitary hormone deficiencies.

2. Hypopituitarism without mass lesions—

A. CONGENITAL HYPOPITUITARISM—This disorder occurs in syndromes such as septo-optic dysplasia and in patients with various gene mutations that cause a progressive loss of

anterior pituitary function in childhood. Prader-Willi syndrome is a genetic disorder where genes on the paternal chromosome 15 are deleted or unexpressed. Kallmann syndrome is caused by various gene mutations that impair the development or migration of GnRH-synthesizing neurons from the olfactory bulb to the hypothalamus. Congenital GH deficiency occurs as an isolated pituitary hormone deficiency in about one-third of cases.

B. ACQUIRED HYPOPITUITARISM—This acquired disorder does not have a visible mass lesion on MRI. It can result from cranial radiation therapy, pituitary surgery, encephalitis, cerebral malaria, hemochromatosis, autoimmunity, or coronary artery bypass grafting (CABG). Bexarotene chemotherapy causes a high rate of pituitary insufficiency with central hypothyroidism. Mitotane therapy for adrenocortical carcinoma causes secondary hypothyroidism in most patients. At least one pituitary hormone deficiency develops in about 25–30% of survivors of moderate to severe traumatic brain injury and in about 55% of survivors of aneurysmal subarachnoid hemorrhage. Some degree of hypopituitarism, most commonly GH deficiency and hypogonadotropic hypogonadism, occurs in one-third of ischemic stroke patients. Other cases of acquired hypopituitarism can be idiopathic or associated with an empty sella on MRI.

C. FUNCTIONAL HYPOPITUITARISM—Opioid use disorder has become a common cause of functional hypopituitarism. About 63% of long-term opioid (including methadone) users develop partial hypogonadotropic hypogonadism. Opioid use also causes secondary adrenal insufficiency in about 15% of patients but is less likely to cause growth hormone or thyroid deficiency. Functional GH deficiency can occur with normal aging, malnutrition, and chronic kidney disease. LH and FSH deficiency with hypogonadotropic hypogonadism occurs in serious illness, malnutrition, anorexia nervosa, alcohol use disorder (alcoholism), Cushing syndrome (spontaneous or iatrogenic), and hyperprolactinemia (drug-induced or spontaneous). Therapy with GnRH agonists (eg, leuprorelin) also causes hypogonadotropic hypogonadism that can persist after therapy is stopped. Partial hypogonadotropic hypogonadism commonly develops in men with normal aging or obesity, since they have serum free testosterone levels that are low or near the lower end of normal reference ranges while serum FSH and LH levels remain normal. Functional hypogonadotropic hypogonadism can occur in both women and men secondary to excessive exercise or weight loss. Women also develop hypothalamic amenorrhea during periods of severe emotional or physical stress. ACTH suppression with functional isolated secondary adrenal insufficiency occurs in patients receiving megestrol acetate, patients on high-dose opioid therapy (15%), and in patients exposed to excess endogenous or exogenous corticosteroids (parenteral, oral, inhaled, or topical). TSH deficiency can be caused by mitotane or bexarotene, resulting in secondary hypothyroidism.

Sheehan syndrome refers to hypopituitarism caused by postpartum pituitary necrosis, usually following severe postpartum uterine hemorrhage. It is usually characterized by postpartum amenorrhea and inability to lactate.

Hypopituitarism can occur acutely, usually with severe secondary adrenal insufficiency that may be fatal unless recognized and treated. Acute hypopituitarism may also be associated with diabetes insipidus. However, hypopituitarism in Sheehan syndrome usually occurs gradually over 10–20 years; the diagnosis is typically delayed an average of 9 years. Manifestations in affected women are typically hyponatremia, hypoglycemia, or anemia. In acute Sheehan syndrome, MRI shows an enlarged pituitary with only a thin rim of enhancement with gadolinium. After 1 year, MRI shows atrophy of the pituitary and a partially empty sella.

► Clinical Findings

When hypopituitarism is caused by a mass lesion or hypophysitis, patients may have headaches or visual field defects. Nonspecific symptoms, such as fatigue, dizziness and hypotension, confusion, cognitive dysfunction, sexual dysfunction, polydipsia, or cold intolerance, can develop.

A. Symptoms and Signs

1. GH (somatotropin) deficiency—Congenital GH deficiency can present in newborns with hypoglycemia, jaundice, and a small penis and later with short stature in childhood.

GH deficiency in adults is often undiagnosed, since maximum height has already been reached and other manifestations are nonspecific. Symptoms vary in severity from mild to severe, resulting in a variable spectrum of nonspecific symptoms that include mild to moderate central obesity, reduced physical and mental energy, impaired concentration and memory, and depression. Patients may also have variably reduced muscle mass, increased low-density lipoprotein (LDL) cholesterol, and reduced cardiac output with exercise. Chronic GH deficiency leads to osteopenia and an increased risk of fractures. When other more recognizable pituitary hormone deficits are present, there is a high likelihood of concurrent GH deficiency.

2. Gonadotropin deficiency (hypogonadotropic hypogonadism)—In gonadotropin deficiency, insufficiencies of LH and FSH cause hypogonadism and infertility.

Congenital gonadotropin deficiency is characterized by partial or complete lack of pubertal development. The sense of olfaction (smell) is entirely normal in 58% (normosmic isolated hypogonadotropic hypogonadism), or hyposmic or anosmic in 42% (Kallmann syndrome). Patients frequently have abnormal genitalia (25%), kidney anomalies (28%), midline craniofacial defects (50%), neurologic deficits (42%), and musculoskeletal malformations. Some affected women have menarche followed by secondary amenorrhea. Some affected males also have congenital adrenal hypoplasia with X-linked inheritance.

Prader-Willi syndrome presents with cryptorchidism, mental retardation, short stature, hyperflexibility, autonomic dysregulation, cognitive impairment, obesity, hypogonadotropic hypogonadism, or primary hypogonadism.

Acquired gonadotropin deficiency is characterized by the gradual loss of facial, axillary, pubic, and body hair.

Men may note diminished libido, erectile dysfunction, muscle atrophy, infertility, and osteopenia. Women have amenorrhea, infertility, and osteoporosis.

3. TSH deficiency—TSH deficiency causes hypothyroidism (see Hypothyroidism, below).

4. ACTH deficiency—Central adrenal insufficiency is caused by ACTH deficiency. There is functional atrophy of the adrenal cortex within 2 weeks of pituitary damage, which results in diminished cortisol. Adrenal mineralocorticoid secretion continues, so manifestations of adrenal insufficiency in hypopituitarism may be less striking than in bilateral adrenal gland destruction (see Primary Adrenal Insufficiency [Addison disease]). Central adrenal insufficiency from pituitary metastases typically presents with nausea, weight loss, and fatigue; these symptoms are often attributed to chemotherapy or to the malignancy itself. Patients with partial ACTH deficiency have some cortisol secretion and may not have symptoms until stressed by illness or surgery.

5. PRL deficiency—This presents in women with failure to lactate in the puerperium.

6. Panhypopituitarism—This condition refers to a deficiency of several or all pituitary hormones. Hypopituitarism typically presents with difficulty breastfeeding and amenorrhea. There may also be hypogonadotropic hypogonadism (62%), diabetes insipidus (54%), headache (50%), hypothyroidism (48%), ACTH deficiency (47%), GH deficiency (37%), and hyperprolactinemia (36%), which clinicians may mistake for a prolactinoma.

7. Hypothalamic damage—This can cause obesity and cognitive impairment. Hypopituitarism occurs but usually along with increased serum levels of PRL. Local tumor effects can cause headache or optic nerve compression with visual field impairment.

B. Laboratory Findings

Initially, there may be hyponatremia and hypoglycemia, with secondary hypoadrenalinism, hypothyroidism, or GH deficiency. Hyponatremia can be caused by hypothyroidism or hypoadrenalinism. Patients with lymphocytic hypophysitis frequently have elevated serum antinuclear or anticytoplasmic antibodies. Patients with hypopituitarism without an established etiology should be screened for hemochromatosis with a serum ferritin or iron and transferrin saturation.

Male hypogonadotropic hypogonadism is diagnosed by drawing blood before 10 AM after an overnight fast in men without an acute or subacute illness. Affected men have a low fasting serum total or free serum testosterone with a low or normal serum LH. A serum PRL is also obtained, since hyperprolactinemia of any cause can result in hypogonadism.

Female hypogonadotropic hypogonadism is suspected in nonpregnant women with amenorrhea or oligomenorrhea, who do not have acute illness, hyperthyroidism, or hyperandrogenism. The serum estradiol is low and the serum FSH is low or normal. In nonpregnant women, a

serum PRL is obtained, since hyperprolactinemia of any cause can result in hypogonadism. In postmenopausal women, the absence of an elevated serum FSH (in a woman not taking estrogen replacement) indicates gonadotropin deficiency.

Central hypothyroidism is diagnosed with a low serum free thyroxine (FT_4) in the setting of pituitary disease. The serum TSH can be low, normal, or even mildly elevated (oddly). Central hypothyroidism can emerge when patients begin GH replacement, so thyroid levels must be monitored in that setting. Patients undergoing pituitary surgery should be assessed for central hypothyroidism preoperatively and again 6 weeks postoperatively.

Central adrenal insufficiency is diagnosed after withholding corticosteroid replacement for at least 18–24 hours. Blood is drawn at 8–9 AM for baseline plasma ACTH and serum cortisol. A serum cortisol less than 3 mcg/dL (80 nmol/L) usually indicates adrenal insufficiency, whereas an 8–9 AM serum cortisol higher than 15 mcg/dL (400 nmol/L) usually excludes adrenal insufficiency. For 8–9 AM cortisol levels between 3 and 15 mcg/dL, a cosyntropin test is often required. For the cosyntropin test, patients should hold any corticosteroid replacement for at least 18–24 hours. At 8–9 AM, blood is drawn for serum cortisol, ACTH, and dehydroepiandrosterone (DHEA); then cosyntropin (synthetic ACTH_{1–24}) 0.25 mg is administered intramuscularly or intravenously. Another serum cortisol is obtained 45 minutes after the cosyntropin injection; a stimulated serum cortisol of less than 20 mcg/dL (550 nmol/L) indicates probable adrenal insufficiency. With gradual pituitary damage and early in the course of ACTH deficiency, patients can have a stimulated serum cortisol of 20 mcg/dL or more (550 nmol/L) but a baseline 8 AM serum cortisol of 5 mcg/dL (138 nmol/L) or less, which is suspicious for adrenal insufficiency. The baseline serum ACTH level is low or normal in secondary hypoadrenalinism, distinguishing it from primary adrenal disease. Serum DHEA is a proxy for ACTH; levels are usually low in patients with secondary adrenal deficiency, helping confirm the diagnosis. Hyponatremia may occur, especially when ACTH and TSH deficiencies are both present.

For patients with signs of secondary adrenal insufficiency (hyponatremia, hypotension, pituitary tumor) but borderline cosyntropin test results, treatment can be instituted empirically and the test repeated at a later date.

GH deficiency in adults is difficult to diagnose, since GH secretion is normally pulsatile and serum GH levels are normally undetectable for much of the day. Also, adults (particularly men) physiologically tend to produce less GH when they are over age 50 or have abdominal obesity. Therefore, pathologic GH deficiency is often inferred by symptoms of GH deficiency in the presence of pituitary destruction or other pituitary hormone deficiencies. GH deficiency is present in 96% of patients with three or more other pituitary hormone deficiencies and a low serum IGF-1. While GH stimulates the production of IGF-1, the serum IGF-1 level is neither a sensitive (about 50%) nor specific test for GH deficiency in adults. While very low serum IGF-1 levels (less than 84 mcg/L) are usually indicative of GH deficiency, they also occur in malnutrition, prolonged

fasting, oral estrogen, hypothyroidism, uncontrolled diabetes mellitus, and liver failure. In GH deficiency (but also in most adults over age 40), exercise-stimulated serum GH levels remain at less than 5 ng/mL and usually fail to rise.

Provocative GH stimulation testing to help diagnose adult GH deficiency has a sensitivity of only 66%. Therefore, a therapeutic trial of GH therapy should be considered for symptomatic patients who have either a serum IGF-1 less than 84 mcg/L or three other pituitary hormone deficiencies.

Provocative GH-stimulation tests are sometimes indicated or required for insurance coverage of GH therapy. In the absence of a serum IGF-1 level less than 84 mcg/L or multiple other pituitary hormone deficiencies, provocative GH-stimulation testing may be indicated for the following patients: (1) young adult patients who have completed GH therapy for childhood GH deficiency and have achieved maximal linear growth; (2) patients who have a hypothalamic or pituitary tumor or who have received surgery or radiation therapy to these areas; and (3) patients who have had prior head trauma, cerebrovascular accident, or encephalitis. When required, such testing usually entails measuring serum GH following provocative stimuli. The single-dose oral macimorelin (Macrilen) GH stimulation test involves the oral administration of macimorelin (a GH secretagogue) to a fasting individual at a dose of 0.5 mg/kg body weight. Blood samples for GH are drawn immediately prior to administration and then at 30, 45, 60, and 90 minutes afterward. A maximum serum GH level below 5.1 ng/mL suggests GH deficiency with 92% sensitivity and 96% specificity. The glucagon stimulation test is a practical alternative to traditional provocative GH stimulation testing to diagnose pathologic GH deficiency or functional GH deficiency due to aging or obesity. It should not be given to patients who are malnourished or who have not eaten for over 48 hours.

C. Imaging

MRI may show hypoplasia or agenesis of the olfactory bulbs in 75% of cases of Kallmann syndrome and in 8% of patients with normosmic hypogonadotropic hypogonadism. MRI typically shows enlargement of the pituitary gland or pituitary stalk with intense enhancement after gadolinium in lymphocytic hypophysitis. MRI shows pituitary enlargement in 75% of cases of ipilimumab-associated hypophysitis but only 25% of cases of anti-PD-1 agent-induced hypophysitis. MRI is not warranted in cases of functional hypopituitarism associated with severe obesity, drugs, or nutritional disorders.

Differential Diagnosis

The failure to enter puberty may simply reflect a constitutional delay in growth and puberty. Secondary adrenal insufficiency may persist for many months following high-dose corticosteroid therapy and may also be seen with inhaled or topical corticosteroid therapy.

Reversible, second hypothyroidism with suppression of TSH and T_4 can be caused by severe illness, hyperthyroxinemia, and administration of triiodothyronine, mitotane, or

bexarotene, resulting in temporary central hypothyroidism. Corticosteroids and megestrol reversibly suppress endogenous ACTH and cortisol secretion.

GH deficiency occurs normally with aging and physiologically with obesity (reversible with sufficient weight loss). Very low serum IGF-1 levels can be seen with prolonged fasting, malnutrition, liver failure, hypothyroidism, and uncontrolled diabetes mellitus.

Complications

During a stressful illness, patients with untreated hypoadrenalinism may become febrile and comatose and die of hyponatremia and shock.

Among patients with craniopharyngiomas, diabetes insipidus is found in 16% preoperatively and in 60% postoperatively. Hyponatremia often presents abruptly during the first 2 weeks following any pituitary surgery. Conventional radiation therapy for intracranial disorders can result in an increased incidence of small vessel ischemic strokes, second tumors and damaged hypothalamic-pituitary function.

Adults with GH deficiency have experienced an increased cardiovascular morbidity. Rarely, acute hemorrhage may occur in large pituitary tumors, manifested by rapid loss of vision, headache, and evidence of acute pituitary failure (pituitary apoplexy) requiring emergency decompression of the sella.

Treatment

A. Corticosteroid Replacement

Long-term therapy is initiated with hydrocortisone 10–25 mg orally in the morning and 5–15 mg in the late afternoon. Other corticosteroids may be used; the dosing and timing must be individually tailored. No mineralocorticoid replacement is required. See Corticosteroid Replacement Therapy—Primary Adrenal Insufficiency (Addison Disease) below.

B. Thyroid Hormone Replacement

Levothyroxine is given to correct hypothyroidism only after the patient is assessed for cortisol deficiency or is already receiving corticosteroids. The typical maintenance dose is about 1.6 mcg/kg body weight, averaging 125 mcg daily with a wide range of 25–300 mcg daily. Assessment of serum TSH is useless for monitoring patients with hypopituitarism. The optimal replacement dose of levothyroxine is determined clinically by raising or lowering the dose, according to the patient's symptoms and clinical examination, until an optimal dose is found. In patients receiving clinically optimal levothyroxine replacement, serum FT_4 levels are usually in the mid to high-normal range. Some patients do not feel clinically euthyroid until they receive levothyroxine in doses at which the serum FT_4 levels are mildly elevated; however, serum T_3 or FT_3 levels should be in the low-normal range. During pregnancy, clinical status and serum FT_4 or total T_4 levels need to be monitored frequently, since higher doses of levothyroxine are usually required.

C. Gonadotropin Hormone Replacement

Hyperprolactinemia-related hypogonadotropic hypogonadism improves or resolves with treatment. Sex hormone replacement may be required. See Male Hypogonadism and Female Hypogonadism.

Women with panhypopituitarism have profound androgen deficiency caused by the combination of both secondary hypogonadism and adrenal insufficiency. When serum DHEA levels are less than 400 ng/mL, women may also be treated with compounded USP-grade DHEA 50 mg/day orally. DHEA therapy tends to increase pubic and axillary hair and may modestly improve libido, alertness, stamina, and overall psychological well-being.

For men with oligospermia, human chorionic gonadotropin (hCG) (equivalent to LH) may be given at a dosage of 2000–3000 units intramuscularly three times weekly and testosterone replacement discontinued. The dose of hCG is adjusted to normalize serum testosterone levels. After 6–12 months of hCG treatment, if the sperm count remains low, hCG injections are continued along with injections of follitropin beta (synthetic recombinant FSH) or urofollitropins (urine-derived FSH). An alternative for patients with an intact pituitary is the use of leuproreotide (GnRH analog) by intermittent subcutaneous infusion. With treatment, testicular volumes increase within 5–12 months, and some spermatogenesis occurs in most cases. With persistent treatment and the use of intracytoplasmic sperm injection for some cases, the pregnancy success rate is about 70%. Men often feel better during hCG therapy than during testosterone replacement. Therefore, some men may elect to continue hCG therapy long term.

Clomiphene, 25–50 mg/day orally, can sometimes stimulate men's own pituitary gonadotropins (when their pituitary is intact), thereby increasing testosterone and sperm production. For fertility induction in females, ovulation may be induced with clomiphene, 50–100 mg/day orally for 5 days every 2 months. Ovulation induction with FSH and hCG can induce multiple births and should be used only by those experienced with their administration.

D. Human Growth Hormone (hGH) Replacement

Symptomatic adults with GH deficiency may be treated with subcutaneous recombinant human growth hormone (rhGH, somatropin) injections, 0.2 mg/day (0.6 international units/day), administered three times weekly. The dosage of rhGH is increased every 2–4 weeks by increments of 0.1 mg (0.3 international units) until side effects occur or a sufficient salutary response and a normal serum IGF-1 level are achieved. In adults, if the desired effects (eg, improved energy and mentation, reduction in visceral adiposity) are not seen within 3–6 months at maximum tolerated dosage, rhGH therapy is discontinued. Therapy with hGH can bring out central hypothyroidism, so serum FT₄ levels require monitoring when beginning hGH therapy.

RhGH may be safely administered to pregnant women with hypopituitarism at their usual pregestational dose during the first trimester, tapering the dose during the

second trimester, and discontinuing rhGH during the third trimester.

Oral estrogen replacement reduces hepatic IGF-1 production. Therefore, prior to commencing rhGH therapy, oral estrogen should be changed to transdermal or transvaginal estradiol.

Treatment of adult GH deficiency usually improves the patient's overall quality of life, with better emotional sense of well-being, increased muscle mass, and decreased visceral fat and waist circumference. Long-term treatment with rhGH does not appear to affect mortality.

Side effects of rhGH therapy may include peripheral edema, hand stiffness, arthralgias and myalgias, paresthesias, carpal tunnel syndrome, tarsal tunnel syndrome, headache, pseudotumor cerebri, gynecomastia, hypertension, and proliferative retinopathy. Treatment with rhGH can also cause sleep apnea, insomnia, dyspnea, sweating, and fatigue. Side effects usually remit promptly after a sufficient reduction in dosage. Replacement therapy with rhGH does not increase the risk of any malignancy or the regrowth of pituitary or brain neoplasms; serum IGF-1 levels should be kept in the normal range.

GH should not be administered during critical illness, since administration of very high doses of rhGH increased mortality in patients receiving intensive care. *There is currently no proven role for GH replacement for the physiologic GH deficiency that is seen with abdominal obesity or normal aging.*

E. Other Treatment

Selective transsphenoidal surgery is usually performed to resect non-prolactinoma pituitary masses and Rathke cleft cysts that cause local symptoms or hypopituitarism. Such surgery reverses hypopituitarism in a minority of cases. Patients with lymphocytic hypophysitis have been treated with corticosteroid therapy and other immunosuppressants without much response and without reversing hypopituitarism.

▶ Prognosis

Functionally, most patients with hypopituitarism do well with hormone replacement. Men with infertility who are treated with hCG/FSH or GnRH are likely to resume spermatogenesis if they have had sexual maturation and have descended testicles with a baseline serum inhibin B level over 60 pg/mL. Women under age 40 years with infertility from hypogonadotropic hypogonadism can usually have successful ovulation induction.

Hypopituitarism resulting from a pituitary tumor may be reversible with dopamine agonists for prolactinomas (see Prolactinoma, below) or with careful selective resection of the tumor. Spontaneous recovery from hypopituitarism associated with pituitary stalk thickening has been reported. Patients can also recover from functional hypopituitarism due to excessive exercise or weight loss if they greatly reduce exercise and gain weight; about half of men regain normal serum testosterone levels. Spontaneous reversal of idiopathic isolated

hypogonadotropic hypogonadism occurs in about 10% of patients after several years of hormone replacement therapy (HRT). However, hypopituitarism is usually permanent, and long-term HRT is ordinarily required.

Patients with hypopituitarism have an increased mortality risk, particularly women and those in whom diagnosis was made at a younger age, who have a craniopharyngioma, or who required transcranial surgery or radiation therapy. There is also an increased risk of death from infections with adrenal crisis in patients with untreated secondary insufficiency. Some pituitary tumors are locally invasive. Asymptomatic Rathke cleft cysts may not require surgery but do require endocrine, ophthalmic, and scan surveillance.

- de Vries F et al. Opioids and their endocrine effects: a systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2020;105:1020. [PMID: 31511863]
- Dwyer AA et al. Functional hypogonadotropic hypogonadism in men: underlying neuroendocrine mechanisms and natural history. *J Clin Endocrinol Metab*. 2019;104:3403. [PMID: 31220265]
- Gubbi S et al. Hypophysitis: an update on the novel forms, diagnosis and management of disorders of pituitary inflammation. *Best Pract Res Clin Endocrinol Metab*. 2019;33:101371. [PMID: 31866206]
- Lu J et al. Immune checkpoint inhibitor-associated pituitary-adrenal dysfunction. A systematic review and meta-analysis. *Cancer Med*. 2019;8:7503. [PMID: 31679184]
- Melmed S. Pituitary-tumor endocrinopathies. *N Engl J Med*. 2020; 382:937. [PMID: 32130815]
- Molitch ME. Diagnosis and treatment of pituitary adenomas: a review. *JAMA*. 2017;317:516. [PMID: 28170483]

CENTRAL DIABETES INSIPIDUS



ESSENTIALS OF DIAGNOSIS

- ▶ Antidiuretic hormone (ADH) deficiency with polyuria (2–20 L/day) and polydipsia.
- ▶ Hypernatremia occurs if fluid intake is inadequate.

General Considerations

Central diabetes insipidus is an uncommon disease caused by a deficiency in vasopressin (ADH) from the posterior pituitary.

Primary central diabetes insipidus (without an identifiable lesion noted on MRI of the pituitary and hypothalamus) accounts for about one-third of all cases of diabetes insipidus. Familial diabetes insipidus occurs as a dominant genetic trait with symptoms developing at about 2 years of age. Central diabetes insipidus may also be idiopathic or due to autoimmunity against hypothalamic arginine vasopressin (AVP)-secreting cells. Reversible central diabetes insipidus can occur with administration of ketamine, temozolomide, or the anti-PD-L1 monoclonal antibody avelumab, and in the myelodysplastic preleukemic phase of acute myelogenous leukemia.

Secondary central diabetes insipidus is most commonly due to damage to the hypothalamus or pituitary stalk by tumor, hypophysitis, infarction, hemorrhage, anoxic encephalopathy, or surgical or head trauma. Less commonly, central diabetes insipidus is caused by infection (eg, encephalitis, tuberculosis, syphilis) or granulomas (sarcoidosis or Langerhans cell granulomatosis). Metastases to the pituitary are more likely to cause diabetes insipidus (33%) than are pituitary adenomas (1%).

► Clinical Findings

A. Symptoms and Signs

The symptoms of the disease are intense thirst, especially with a craving for ice water, with the volume of ingested fluid varying from 2 L to 20 L daily, and polyuria, with large urine volumes and low urine specific gravity (usually less than 1.006 with ad libitum fluid intake). The urine is otherwise normal. Partial diabetes insipidus presents with less intense symptoms and should be suspected in patients with enuresis. Most patients with diabetes insipidus are able to maintain fluid balance by continuing to ingest large volumes of water. However, in patients without free access to water or with a damaged hypothalamic thirst center and altered thirst sensation, diabetes insipidus may present with hypernatremia and dehydration. Diabetes insipidus is aggravated by administration of high-dose corticosteroids, which increases renal free water clearance.

B. Laboratory Findings

Diagnosis of central diabetes insipidus is a clinical one; there is no single diagnostic laboratory test. Evaluation should include a 24-hour urine collection for volume and creatinine. A urine volume of less than 2 L/24 h (in the absence of hypernatremia) rules out diabetes insipidus. The patient can be tested during ad libitum fluid intake. A random urine is tested for osmolality. Blood testing includes plasma vasopressin and serum glucose, urea nitrogen, calcium, potassium, sodium, and uric acid.

Plasma AVP levels are usually low (below 1 pg/mL) with both central diabetes insipidus and primary polyuria, whereas plasma AVP levels are normal or elevated (more than 2.5 pg/mL) with nephrogenic diabetes insipidus. Plasma osmolality of 300 mOsm/kg or more implies either central or nephrogenic diabetes insipidus, whereas plasma osmolality of 280 mOsm/kg or less implies primary polydipsia as the diagnosis. Urine osmolality is low (300 mOsm/L or lower) in all three polyuric conditions and is not a helpful test. Hyperuricemia occurs frequently with both central and nephrogenic diabetes insipidus, whereas it is uncommon with primary polydipsia.

A supervised “vasopressin challenge test” may be done: Desmopressin acetate 0.05–0.1 mL (5–10 mcg) intranasally (or 1 mcg subcutaneously or intravenously) is given, with measurement of urine volume for 12 hours before and 12 hours after administration. A serum sodium is obtained at baseline, 12 hours after the desmopressin, and immediately if symptoms of hyponatremia develop. Patients with central diabetes insipidus notice a distinct reduction in

thirst and polyuria; serum sodium usually remains normal. The dosage of desmopressin is doubled if the response is marginal. In patients with primary polydipsia, a desmopressin challenge causes no significant reduction in polydipsia. Patients with nephrogenic diabetes insipidus show no response in polydipsia or urine volume.

Another test to distinguish central diabetes insipidus from primary polydipsia involves the carefully supervised hypertonic 3% saline-stimulated measurement of plasma copeptin, the C-terminal fragment of pre-pro-arginine vasopressin. Hypertonic 3% saline is administered intravenously as a 250 mL bolus, followed by a continuous infusion rate of 0.15 mL/kg/min. Plasma sodium is measured stat every 30 minutes; when the plasma sodium level reaches 150 mmol/L, blood is drawn for plasma copeptin. A level 4.9 pmol/L or less helps confirm the diagnosis of central diabetes insipidus.

C. Imaging

The normal posterior “bright spot” seen on the MRI T1-weighted image is undetectable or small with central diabetes insipidus, whereas it is normal in primary polydipsia and nephrogenic diabetes insipidus. MRI can also detect pathology responsible for central diabetes insipidus.

Differential Diagnosis

Central diabetes insipidus must be distinguished from polyuria caused by psychogenic polydipsia, diabetes mellitus, Cushing syndrome, hypercalcemia, hypokalemia, and nocturnal polyuria of Parkinson disease.

Vasopressinase-induced diabetes insipidus may be seen in the last trimester of pregnancy, associated with oligohydramnios, preeclampsia, or liver dysfunction, and in the puerperium. Maternal circulating vasopressin is destroyed by placental vasopressinase; however, synthetic desmopressin is unaffected.

Nephrogenic diabetes insipidus is caused by unresponsiveness of the kidney tubules to the normal secretion of vasopressin. A congenital form is familial and transmitted as an X-linked trait; it is caused by defective expression of renal vasopressin V2 receptors or vasopressin-sensitive water channels. Adults often also have hyperuricemia. Acquired forms are usually less severe and occur in pyelonephritis, renal amyloidosis, myeloma, potassium depletion, Sjögren syndrome, sickle cell anemia, chronic hypercalcemia, or recovery from acute tubular necrosis. Certain drugs (eg, corticosteroids, diuretics, demeclocycline, lithium, foscarnet, or methicillin) may induce nephrogenic diabetes insipidus.

Complications

If water is not readily available, the excessive output of urine will lead to severe dehydration and worsening hypernatremia. Patients with an impaired thirst mechanism are very prone to hypernatremia, as are those with impaired mentation who forget to take their desmopressin. Excessive desmopressin acetate can induce water intoxication and hyponatremia.

Treatment

Mild cases of diabetes insipidus require no treatment other than adequate fluid intake. Reduction of aggravating factors (eg, corticosteroids) will improve polyuria.

Desmopressin acetate is the treatment of choice for central diabetes insipidus and for vasopressinase-induced diabetes insipidus associated with pregnancy or the puerperium. Desmopressin acetate (100 mcg/mL solution) is given intranasally every 12–24 hours as needed for thirst and polyuria. It may be administered via metered-dose nasal inhaler containing 0.1 mL (10 mcg/spray) or via a calibrated rhinal tube. The starting dose is one metered-dose spray or 0.05–0.1 mL every 12–24 hours, and the dose is then individualized according to response. Desmopressin nasal may cause rhinitis or conjunctivitis. If the generic preparation is ineffective, switching to the desmopressin brand may provide relief.

Oral desmopressin is initiated at 0.05 mg twice daily and increased to a maximum of 0.4 mg every 8 hours, if required. Oral desmopressin is particularly useful for patients in whom rhinitis or conjunctivitis develops from the nasal preparation. Gastrointestinal symptoms, asthenia, and mild increases in hepatic enzymes can occur with the oral preparation. Sublingual desmopressin, 60, 120, or 250 mcg, is not available in the United States; hyponatremia has been reported with this formulation.

Desmopressin can be given intravenously, intramuscularly, or subcutaneously in doses of 1–4 mcg every 12–24 hours as needed.

Desmopressin may cause hyponatremia, but this is uncommon if minimum effective doses are used and the patient allows thirst to occur every 1–2 days. Desmopressin can sometimes cause agitation, emotional changes, and depression with an increased risk of suicide. Patients should be monitored by family, friends, and medical staff when desmopressin therapy is started.

Prognosis

Central diabetes insipidus after pituitary surgery or head trauma usually remits after days to weeks but may be permanent if the hypothalamus or upper pituitary stalk is damaged.

Chronic central diabetes insipidus is ordinarily more an inconvenience than a dire medical condition. Hypernatremia can occur, especially when the hypothalamic thirst center is damaged, but diabetes insipidus does not otherwise reduce life expectancy, and the prognosis is that of the underlying disorder. Treatment with desmopressin allows normal sleep and activity.

Christ-Crain M et al. Copeptin in the differential diagnosis of hypotonic polyuria. *J Endocrinol Invest*. 2020;43:21. [PMID: 31368050]

Devuyst F et al. Central diabetes insipidus and pituitary stalk thickening in adults: distinction of neoplastic from non-neoplastic lesions. *Eur J Endocrinol* 2020;181:95. [PMID: 32530258]

Gubbi S et al. Diagnostic testing for diabetes insipidus. *Endotext* [Internet]. 2019. [PMID: 30779536]

ACROMEGALY & GIGANTISM



ESSENTIALS OF DIAGNOSIS

- ▶ Pituitary neuroendocrine tumor.
- ▶ **Gigantism** before closure of epiphyses.
- ▶ **Acromegaly:** excessive growth of hands, feet, jaw, internal organs.
- ▶ Amenorrhea, hypertension, headaches, visual field loss, weakness.
- ▶ Soft, doughy, sweaty handshake.
- ▶ Elevated serum IGF-1.

► General Considerations

GH exerts much of its growth-promoting effects by stimulating the release of IGF-1 from the liver and other tissues.

Acromegaly is a rare condition, with a yearly incidence of about 10 cases per million. It is nearly always caused by a pituitary adenoma. About 70% are macroadenomas (1 cm or larger) when diagnosed. These tumors may be locally invasive, particularly into the cavernous sinus. Less than 1% are malignant. Acromegaly is usually sporadic but may rarely be familial, with less than 3% being due to multiple endocrine neoplasia (MEN) types 1 or 4. Acromegaly may also be seen rarely in McCune-Albright syndrome and Carney complex. Acromegaly is very occasionally caused by ectopic secretion of GHRH or GH secreted by a neuroendocrine tumor or lymphoma.

► Clinical Findings

A. Symptoms and Signs

Excessive GH causes tall stature and gigantism if it occurs in youth, before closure of epiphyses. Afterward, acromegaly develops. The manifestations of acromegaly usually present insidiously; median time to diagnosis after symptom onset is 10 years. The hands enlarge and a doughy, moist handshake is characteristic. The fingers widen, causing patients to enlarge their rings. Carpal tunnel syndrome is common. The feet also grow, particularly in shoe width. Facial features coarsen since the bones and sinuses of the skull enlarge; hat size increases. The mandible becomes more prominent, causing prognathism and malocclusion. Tooth spacing widens. Older photographs of the patient can be a useful comparator.

Macroglossia occurs, as does hypertrophy of pharyngeal and laryngeal tissue; this causes a deep, coarse voice and sometimes makes intubation difficult. Snoring and obstructive sleep apnea are common. A goiter may be noted. Hypertension (50%) and cardiomegaly are common. At diagnosis, about 10% of acromegalic patients have a dilated left ventricle and heart failure with reduced ejection fraction. Weight gain is typical, particularly of muscle and bone. Insulin resistance is usually present and frequently causes diabetes mellitus (30%). Polyarticular arthralgias and degenerative arthritis are present in about

70% of patients. Overgrowth of vertebral bone can cause spinal stenosis. Colon polyps are found in about 30%, especially in patients with skin papillomas. The skin may also manifest hyperhidrosis, thickening, cystic acne, skin tags, and acanthosis nigricans.

GH-secreting pituitary tumors usually cause some hypogonadism, either by cosecretion of PRL or by direct pressure upon normal pituitary tissue. Decreased libido and erectile dysfunction are common in men and irregular menses or amenorrhea occur in women. Women who become pregnant have an increased risk of gestational diabetes and hypertension. Secondary hypothyroidism sometimes occurs; hypoadrenalinism is unusual. Headaches are frequent. Temporal hemianopia may occur as a result of the optic chiasm being impinged by suprasellar extension of the tumor.

B. Laboratory Findings

For screening purposes, a random serum IGF-1 can be obtained. If it is normal for age, acromegaly is ruled out.

For further evaluation, the patient should be fasting for at least 8 hours (except for water), not be acutely ill, and not have exercised on the day of testing. Assay for the following: serum GH, IGF-1 (increased and usually over five times normal in acromegaly), PRL (cosecreted by many GH-secreting tumors), glucose (diabetes mellitus is common in acromegaly), liver enzymes and serum creatinine or urea nitrogen (liver failure or kidney disease can misleadingly elevate GH), serum calcium (to exclude hyperparathyroidism), serum inorganic phosphorus (frequently elevated), serum free T₄, and TSH (secondary hypothyroidism is common in acromegaly; primary hypothyroidism may increase PRL). Acromegaly is excluded if any serum GH is less than 1 mcg/L; however, many normal individuals can have a serum GH above this level. Therefore, the glucose suppression test is usually performed. Glucose syrup (100 g) is administered orally, and serum GH is measured 60 minutes afterward; acromegaly is excluded if the serum GH is suppressed to below 0.4 mcg/L with an ultrasensitive GH assay. The serum IGF-1 and glucose-suppressed GH are usually complementary tests; however, disparities between the two occur in up to 30% of patients.

C. Imaging

MRI shows a pituitary tumor in over 90% of acromegalic patients. MRI is generally superior to CT scanning, especially in the postoperative setting. Radiographs of the skull may show an enlarged sella and thickened skull. Radiographs may also show tufting of the terminal phalanges of the fingers and toes. A lateral view of the foot shows increased thickness of the heel pad.

► Differential Diagnosis

Active acromegaly must be distinguished from familial coarse features, large hands and feet, and isolated prognathism and from inactive ("burned-out") acromegaly in which there has been a spontaneous remission due to infarction of the pituitary adenoma. GH-induced gigantism must be differentiated from familial tall stature and from aromatase deficiency.

Misleadingly high serum GH levels can be caused by exercise or eating just prior to the test; acute illness or agitation; liver failure or kidney disease; malnourishment; diabetes mellitus; or concurrent treatment with oral estrogens, beta-blockers, or clonidine. Acromegaly can be difficult to diagnose during pregnancy, since the placenta produces GH and commercial GH assays may not be able to distinguish between pituitary and placental GH. During normal adolescence, serum IGF-1 is usually elevated and GH may fail to be suppressed.

▶ Complications

Complications include hypopituitarism, hypertension, hyperglycemia, cardiac enlargement, heart failure, and colon polyps. Arthritis of hips, knees, and spine can be troublesome as can carpal tunnel syndrome. Cord compression may occur. Visual field defects may be severe and progressive. Acute loss of vision or cranial nerve palsy may occur if the tumor undergoes spontaneous hemorrhage and necrosis (pituitary apoplexy).

▶ Treatment

A. Pituitary Microsurgery

Transsphenoidal pituitary surgery achieves a remission in about 70% of patients followed over 3 years. With tumors smaller than 2 cm and GH levels below 50 ng/mL, transsphenoidal pituitary surgery is successful in 80% of patients. Extrasellar extension of the pituitary tumor, particularly cavernous sinus invasion, reduces the likelihood of surgical cure. Transsphenoidal surgery is usually well tolerated, but complications occur in about 12% of patients, including infection, cerebrospinal fluid (CSF) leak, and hypopituitarism.

B. Medications

Acromegalic patients with an incomplete biochemical remission after pituitary surgery may benefit from medical therapy with dopamine agonists, somatostatin analogs, tamoxifen, or pegvisomant.

Cabergoline is the oral dopamine agonist of choice. It is most successful for tumors that secrete both PRL and GH but can also be effective for patients with normal serum PRL levels. Cabergoline may be tried as monotherapy for patients with serum IGF-1 levels above normal but less than 2.5 times the upper limit of normal. Cabergoline will shrink one-third of acromegaly-associated pituitary tumors by more than 50%. It appears to be safe during pregnancy. The initial dose is 0.25 mg orally twice weekly, which is gradually increased to a maximum dosage of 1 mg three times weekly (based on serum GH and IGF-1 levels).

Octreotide LAR and **lanreotide** are long-acting somatostatin analogs that are given by monthly subcutaneous injection. They can achieve serum GH levels below 2 ng/mL in 79% of patients and normal serum IGF-1 levels in 53% of patients.

Raloxifene is a selective estrogen receptor modulator (SERM) that may be useful for persistent acromegaly in men and in women who are postmenopausal or who have had breast cancer. Raloxifene (60 mg orally twice daily)

does not reduce serum GH levels but normalizes serum IGF-1 levels in 46% of patients. Serum testosterone levels increase in men.

Pegvisomant, a GH receptor antagonist, can be helpful for patients resistant to other treatments, especially when there is associated diabetes mellitus. It blocks hepatic IGF-1 production but does not shrink GH-secreting tumors. Pegvisomant therapy produces symptomatic relief and normalizes serum IGF-1 levels in 63% of patients.

C. Stereotactic Radiosurgery

Acromegalic patients who do not achieve a complete remission with transsphenoidal surgery or medical therapy may be treated with stereotactic radiosurgery: linear accelerator (eg, Cyberknife), gamma knife radiosurgery, and proton beam radiosurgery. Following any pituitary radiation therapy, patients are advised to take lifelong daily low-dose aspirin because of the increased risk of small-vessel stroke. Stereotactic radiosurgery to pituitary tumors causes anterior hypopituitarism in 35–60% of patients within 5 years, so patients must have regular monitoring of their pituitary function.

▶ Prognosis

Acromegaly is usually chronic and progressive unless treated. Spontaneous remissions are rare but have been reported following clinical or subclinical apoplexy (hemorrhage) within the tumor. Patients with acromegaly experience increased mortality from cardiovascular disorders and progressive acromegalic symptoms. Those who are treated and have a random serum GH under 1.0 ng/mL or a glucose-suppressed serum GH under 0.4 ng/mL with normal age-adjusted serum IGF-1 levels have reduced morbidity and mortality.

Postoperatively, normal pituitary function is usually preserved. Soft tissue swelling regresses but bone enlargement is permanent. Hypertension frequently persists despite successful surgery. Adjuvant medical therapy is successful in treating patients who are not cured by pituitary surgery. Conventional radiation therapy (alone) produces a remission in about 40% of patients by 2 years and 75% of patients by 5 years after treatment. Gamma knife or cyberknife radiosurgery reduces GH levels an average of 77%, with 20% of patients having a full remission after 12 months. Proton beam radiosurgery produces a remission in about 70% of patients by 2 years and 80% of patients by 5 years. Radiation therapy eventually produces some degree of hypopituitarism in most patients. Conventional radiation therapy may cause some degree of organic brain syndrome and predisposes to small strokes. Patients must receive lifelong follow-up, with regular monitoring of serum GH and IGF-1 levels. Serum GH levels over 5 ng/mL and rising IGF-1 levels usually indicate a recurrent tumor. Most pregnant women with acromegaly do not have an increase in the size of the pituitary tumor and neonatal outcome is unaffected.

Tritos NA et al. All-cause mortality in patients with acromegaly treated with pegvisomant: an ACROSTUDY analysis. Eur J Endocrinol. 2020;182:285. [PMID: 31917681]

HYPERPROLACTINEMIA



ESSENTIALS OF DIAGNOSIS

- ▶ Women: Oligomenorrhea, amenorrhea; galactorrhea; infertility.
- ▶ Men: Hypogonadism; decreased libido and erectile dysfunction; infertility.
- ▶ Elevated serum PRL; PRL is normally elevated during pregnancy.
- ▶ CT or MRI may show a pituitary adenoma.

General Considerations

Some causes of hyperprolactinemia are shown in Table 26–1. Hyperprolactinemia (without a pituitary adenoma) may

Table 26–1. Causes of hyperprolactinemia.

Physiologic Causes	Pharmacologic Causes	Pathologic Causes
Assay interference	Amoxapine	Acromegaly
Exercise	Amphetamines	Chronic chest wall stimulation (thoracotomy, augmentation or reduction mammoplasty, mastectomy, herpes zoster, chest acupuncture, nipple rings, etc)
Familial (mutant prolactin receptor)	Anesthetic agents	Hypothalamic or pituitary stalk damage
Idiopathic	Antipsychotics (conventional and atypical)	Hypothyroidism
Macroprolactin ("big prolactin")	Androgens	Liver disease
Nipple stimulation	Butyrophenones	Multiple sclerosis
Neonatal	Cimetidine (not famotidine or nizatidine)	Optic neuromyelitis
Pregnancy	Cocaine use or withdrawal	Prolactin-secreting tumors
Sleep (REM phase)	Domperidone	Pseudocyesis (false pregnancy)
Stress (trauma, surgery)	Estrogens	Kidney failure (especially with zinc deficiency)
Suckling	Hydroxyzine	Spinal cord lesions
	Licorice (real)	Systemic lupus erythematosus
	Locaserin	
	MAO inhibitors	
	Methyldopa	
	Metoclopramide	
	Opioids	
	Nicotine	
	Phenothiazines	
	Protease inhibitors	
	Progesterins	
	Reserpine	
	SSRIs	
	Tricyclic antidepressants	
	Verapamil	

MAO, monoamine oxidase; REM, rapid eye movement; SSRIs, selective serotonin reuptake inhibitors.

also be familial. PRL-secreting pituitary tumors (prolactinomas) are the most common secretory pituitary tumor; they are usually sporadic but may rarely be familial as part of MEN type 1 or 4. Most are microadenomas (smaller than 1 cm), which are more common in women and typically do not grow even with pregnancy or oral contraceptives. However, aggressive macroprolactinomas (larger than 1 cm) are more common in men and can spread into the cavernous sinuses and suprasellar areas; rarely, they may erode the floor of the sella to invade the paranasal sinuses.

Clinical Findings

A. Symptoms and Signs

Hyperprolactinemia may cause hypogonadotropic hypogonadism and reduced fertility. Men usually have diminished libido and erectile dysfunction that may not respond to testosterone replacement; gynecomastia sometimes occurs.

About 90% of premenopausal women with prolactinomas experience amenorrhea, oligomenorrhea, or infertility. Estrogen deficiency can cause decreased vaginal lubrication, irritability, anxiety, and depression. Galactorrhea (lactation in the absence of nursing) is common. During pregnancy, clinically significant enlargement of a microprolactinoma (smaller than 10 mm) occurs in less than 3%; clinically significant enlargement of a macroprolactinoma occurs in about 30%.

Pituitary prolactinomas may cosecrete GH and cause acromegaly. Large tumors may cause headaches, visual symptoms, and pituitary insufficiency.

Aside from pituitary tumors, some women secrete an abnormal form of PRL that appears to cause peripartum cardiomyopathy. Suppression of PRL secretion with dopamine agonists can reverse the cardiomyopathy.

B. Laboratory Findings

An elevated serum prolactin level should be verified with a repeat determination, ideally in a different laboratory. Biotin supplements can cause falsely low serum PRL measurements; patients should not take a biotin supplement for at least 8 hours before the blood draw. Evaluate for conditions known to cause hyperprolactinemia, particularly pregnancy (serum hCG), hypothyroidism (serum FT₄ and TSH), kidney disease (blood urea nitrogen [BUN] and serum creatinine), cirrhosis (liver tests), and hyperparathyroidism (serum calcium). Screen for acromegaly with a random serum IGF-1 level. Men are evaluated for hypogonadism with serum total and free testosterone, LH, and FSH. Women who have amenorrhea are assessed for hypogonadism with serum estradiol, LH, and FSH. Patients with macroprolactinomas or manifestations of possible hypopituitarism should be evaluated for hypopituitarism. Patients with hyperprolactinemia who are relatively asymptomatic and have no apparent cause for hyperprolactinemia should have an assay for macroprolactinemia, which is an increased circulating level of a high molecular weight PRL that is biologically inactive but is detected on assays.

C. Imaging

Patients with hyperprolactinemia not induced by drugs, hypothyroidism, or pregnancy should be examined by pituitary MRI. Small prolactinomas may be demonstrated, but clear differentiation from normal variants is not always possible. In the event that a woman with a macroadenoma becomes pregnant and elects not to take dopamine agonists during her pregnancy, MRI is usually not performed since the normal pituitary grows during pregnancy. However, if visual-field defects or other neurologic symptoms develop in a pregnant woman, a limited MRI study should be done, focusing on the pituitary without gadolinium contrast.

Differential Diagnosis

The differential diagnosis for galactorrhea includes the small amount of breast milk that can normally be expressed from the nipple in many parous women. Nipple stimulation from nipple rings, chest surgery, or acupuncture can cause galactorrhea; serum PRL levels may be normal or minimally elevated. Some women can have idiopathic galactorrhea with normal serum PRL levels. Normal breast milk may be various colors besides white. However, bloody galactorrhea requires evaluation for breast cancer.

About 40% of nonfunctional pituitary macroadenomas produce some degree of hyperprolactinemia. These and other lesions and malignancies can be misdiagnosed as prolactinomas. One distinguishing characteristic is that the serum PRL is usually only marginally elevated in the latter tumors, whereas with pituitary macroadenomas the serum PRL typically exceeds 100 mcg/L.

Pregnant women have high serum PRL levels, with physiological hyperplastic enlargement of the pituitary on MRI. Increased pituitary size is a normal variant in young women. Primary hypothyroidism can cause hyperprolactinemia and hyperplasia of the pituitary that can be mistaken for a pituitary adenoma. Macroadenoma occurs in 3.7% of the general population and accounts for 10–25% of all cases of hyperprolactinemia; pituitary MRI shows a nonpathological abnormality in 22% of such patients.

Treatment

Medications known to increase PRL should be stopped if possible (Table 26–1). Hyperprolactinemia due to hypothyroidism is corrected by levothyroxine.

Women with microadenomas who have amenorrhea or are desirous of contraception may safely take estrogen replacement or oral contraceptives—there is minimal risk of stimulating enlargement of the microadenoma. Patients with infertility and hyperprolactinemia may be treated with a dopamine agonist in an effort to improve fertility. Women with amenorrhea who elect to receive no treatment have an increased risk of developing osteoporosis; such women require periodic bone densitometry.

Pituitary macroadenomas have a higher risk of progressive growth, particularly during estrogen or testosterone HRT or during pregnancy. Therefore, patients with macroadenomas should not be treated with HRT or

oral contraceptives unless they are in remission with dopamine agonist medication or surgery.

Pregnant women with macroadenomas should continue to receive treatment with dopamine agonists throughout the pregnancy to prevent tumor growth. If dopamine agonists are not used during pregnancy in a woman with a macroadenoma, visual field testing is required in each trimester. Measurement of PRL is not useful surveillance for tumor growth due to the fact that PRL increases greatly during normal pregnancy.

A. Dopamine Agonists

Dopamine agonists (cabergoline, bromocriptine, or quinagolide) are the initial treatment of choice for patients with giant prolactinomas and those with hyperprolactinemia desiring restoration of normal sexual function and fertility. Cabergoline is the most effective and usually the best-tolerated ergot-derived dopamine agonist. Begin with 0.25 mg orally once weekly for 1 week, then 0.25 mg twice weekly for the next week, then 0.5 mg twice weekly. Further dosage increases may be required monthly, based on serum PRL levels, up to a maximum of 1.5 mg twice weekly. Bromocriptine (1.25–20 mg/day orally) is an alternative. Women who experience nausea with oral preparations may find relief with deep vaginal insertion of cabergoline or bromocriptine tablets; vaginal irritation sometimes occurs. Patients whose tumor is resistant to one dopamine agonist may be switched to another in an effort to induce a remission.

Dopamine agonists are given at bedtime to minimize side effects of fatigue, nausea, dizziness, and orthostatic hypotension, which occur in up to 50% of patients. These symptoms usually improve with dosage reduction and continued use. Dopamine agonists can cause a variety of psychiatric side effects (particularly depression, impulse control disorder, and hypersexuality) that are not dose related and may take weeks to resolve once the drug is discontinued. In doses used for prolactinomas, dopamine agonists have not caused cardiac valvulopathy.

Dopamine agonists do not increase the risk of miscarriage or teratogenicity. Pregnant women with microadenomas may safely stop treatment during pregnancy and breastfeeding. However, macroadenomas may enlarge significantly during pregnancy; if therapy is withdrawn, patients must be monitored with serum PRL determinations and computer-assisted visual fields. Women with macroadenomas who have responded to dopamine agonists may safely receive oral contraceptives as long as they continue receiving dopamine agonist therapy.

B. Surgical Treatment

Transsphenoidal pituitary surgery may be urgently required for large tumors undergoing apoplexy or those severely compromising visual fields. It is also used electively for patients who do not tolerate or respond to dopamine agonists. Transsphenoidal pituitary surgery is generally well tolerated, with a mortality rate of less than 0.5%. For pituitary microadenomas, skilled neurosurgeons are successful in normalizing PRL in 87% of patients and some patients prefer surgery to long-term therapy with dopamine agonists.

Complications, such as CSF leakage, meningitis, stroke, or visual loss, occur in about 3% of cases; sinusitis, nasal septal perforation, or infection complicates about 6.5% of transsphenoidal surgeries. Diabetes insipidus can occur within 2 days postoperatively but is usually mild and self-correcting. Hyponatremia can occur abruptly 4–13 days postoperatively in 21% of patients; symptoms may include nausea, vomiting, headache, malaise, or seizure. It is treated with free water and hypotonic fluid restriction.

C. Stereotactic Radiosurgery

Stereotactic radiosurgery is seldom required for prolactinomas, since they usually respond to cabergoline or surgery. It is reserved for patients with macroadenomas that are growing despite treatment with dopamine agonists.

D. Chemotherapy

Some patients with aggressive pituitary macroadenomas or carcinomas are not surgical candidates and do not respond to dopamine agonists or radiation therapy. A small percentage of patients with aggressive tumors respond to the addition of temozolamide (150–200 mg/m² orally daily for 5 days of each 28-day cycle) or everolimus to cabergoline. Treatment efficacy is determined by PRL measurement and MRI scanning.

► Prognosis

Pituitary microprolactinomas are typically indolent, and only 15% grow after diagnosis. However, pituitary macroprolactinomas tend to be more aggressive. Prolactinomas generally respond well to dopamine agonist therapy. Ninety percent of patients with prolactinomas experience a fall in serum PRL to 10% or less of pretreatment levels and about 80% of treated patients achieve a normal serum PRL level. Shrinkage of a pituitary adenoma occurs early, but the maximum effect may take up to 1 year. Nearly half of prolactinomas—even massive tumors—shrink more than 50%. During pregnancy, growth of a pituitary prolactinoma occurs in 3% of women with a microprolactinoma and in 23% of those with a macroprolactinoma. If cabergoline is stopped after 2 years of therapy, hyperprolactinemia recurs in 68% of patients with idiopathic hyperprolactinemia, 79% with microprolactinomas, and 84% with macroprolactinomas.

The 10-year recurrence rate is 13% for pituitary macroadenomas after transsphenoidal surgery; pituitary function can be preserved in over 95% of cases. However, the surgical success rate for macroprolactinomas is much lower, and the complication rates are higher.

De Sousa SMC et al. Impulse control disorders in dopamine agonist-treated hyperprolactinemia: prevalence and risk factors. *J Clin Endocrinol Metab*. 2020;105:dgz076. [PMID: 31580439]

Donoho DA et al. The role of surgery in the management of prolactinomas. *Neurosurg Clin N Am*. 2019;30:509. [PMID: 31471058]

Glezer A et al. Prolactinomas in pregnancy: considerations before conception and during pregnancy. *Pituitary*. 2020;23:65. [PMID: 31792668]

Molitch ME. Dopamine agonists and antipsychotics. *Eur J Endocrinol*. 2020;183:C11. [PMID: 32508315]

NONFUNCTIONING PITUITARY ADENOMAS

ESSENTIALS OF DIAGNOSIS

- Clinical and biochemical evaluation for pituitary hormone hypersecretion is negative.
- MRI shows a pituitary microadenoma (< 1 cm) or macroadenoma (≥ 1 cm).
- Headache, visual field compromise, and anterior hypopituitarism are common with macroadenomas.
- Elevated serum PRL with macroadenomas may be due to stalk compression.

► General Considerations

Nonfunctioning pituitary adenomas are benign neuroendocrine neoplasms that do not produce symptoms from hormone oversecretion. Pituitary nonfunctioning adenomas occur more frequently in men than women and are more common with age. Nonfunctioning pituitary microadenomas (smaller than 1 cm) are common, detected as an incidental finding in 4–37% of brain CT or MR imaging.

► Clinical Findings

A. Symptoms and Signs

Nonfunctioning pituitary macroadenomas (1 cm or larger) tend to be more aggressive than functioning pituitary adenomas. Those with nonfunctioning macroadenomas are much more likely to be symptomatic from mass effect with visual field compromise, headache, cranial nerve palsies affecting extraocular muscles, and pituitary apoplexy. Larger macroadenomas frequently cause some hypopituitarism, particularly hypogonadotropic hypogonadism. Nonfunctioning pituitary microadenomas are asymptomatic.

B. Laboratory Findings

1. Pituitary hormone hypersecretion—All patients with a pituitary adenoma require testing for pituitary hormone hypersecretion. Obtain a serum PRL to screen for prolactin hypersecretion; women with hyperprolactinemia are tested for pregnancy with a serum hCG. Testing for Cushing disease or acromegaly should be obtained, if clinically indicated.

2. Anterior hypopituitarism—Men should have following tests: serum free T₄, TSH, morning serum testosterone and free testosterone. Serum LH and FSH should be obtained in men with low serum testosterone, women who are postmenopausal, and younger women with amenorrhea. Serum sodium and glucose should also be obtained in all patients. A serum IGF-1 is drawn to screen for GH deficiency. Younger patients with short stature who have not fused their epiphyses should have a full evaluation for growth hormone deficiency.

3. Pituitary macroadenomas—Patients with a macroadenoma that impinges upon the optic chiasm require formal

visual field testing. A cosyntropin stimulation test is performed for patients with hyponatremia or symptoms of possible hypoadrenalinism.

C. Imaging

Pituitary dynamic contrast-enhanced MRI (3T) is the imaging modality of choice for the evaluation and follow-up of pituitary adenomas. Nonfunctioning pituitary microadenomas that are smaller than 0.5 cm require no further MRI follow-up. For nonfunctioning pituitary adenomas 0.5 cm or larger, repeat MRI is recommended at 6 months, then yearly for 3 years. If no enlargement is noted, MRI surveillance can then be done less frequently.

Differential Diagnosis

About 29% of pituitary adenomas that are initially diagnosed as incidental turn out to have another etiology; mass lesions that can mimic pituitary adenoma include pituitary craniopharyngiomas, gliomas, meningiomas, skull base osteosarcomas, Rathke cysts, lymphocytic hypophysitis, infection, or metastases. Large normal pituitary glands and physiologic pituitary enlargement during primary hypothyroidism or pregnancy should also be considered; serum prolactin levels are elevated in primary hypothyroidism and pregnancy. Hyperprolactinemia also occurs when there is pituitary stalk compression from pituitary macroadenomas and other mass lesions; with pituitary stalk compression, serum prolactin is typically lower than expected for the size of the pituitary mass.

Treatment

Patients with asymptomatic pituitary nonfunctioning microadenomas ordinarily require no treatment. Patients need to be followed closely, however, with periodic MRI surveillance. Surgery is the main treatment option and should be considered for patients whose adenoma is causing mass effect symptoms, premature development of puberty, hormonal deficiencies, or the emergence of symptomatic hormonal hypersecretion. Radiation therapy can be used for select individuals with pituitary macroadenomas.

Prognosis

The prognosis is excellent for patients with nonfunctioning microadenomas smaller than 0.5 cm. Patients with larger nonfunctioning microadenomas also have a very good prognosis, but require follow-up. Transsphenoidal surgery is 65% successful in completely resecting pituitary macroadenomas and improves hypopituitarism in 50%. Surgery reverses visual field compromise in 80% of patients. Adjuvant radiation therapy may be given postoperatively, depending on surgical findings. For nonfunctioning pituitary macroadenomas, the 6-year postoperative recurrence rate has been reported to be 36% following surgery alone and 13% after surgery plus adjuvant radiation therapy.

Petersenn S. Management of aggressive pituitary tumors—a 2019 update. *Horm Metab Res*. 2019;51:755. [PMID: 31826270]

DISEASES OF THE THYROID GLAND

THYROIDITIS



ESSENTIALS OF DIAGNOSIS

Autoimmune thyroiditis

- ▶ Chronic lymphocytic (Hashimoto) thyroiditis is the most common thyroiditis and often progresses to hypothyroidism.
- ▶ Postpartum thyroiditis and subacute lymphocytic thyroiditis (silent thyroiditis) can cause transient hyperthyroidism due to passive release of stored thyroid hormone.
- ▶ Thyroid peroxidase antibodies (TPO Ab) or thyroglobulin antibodies (Tg Ab) are usually high.

Painful subacute thyroiditis (de Quervain thyroiditis)

- ▶ Hallmark is tender thyroid gland with painful dysphagia.
- ▶ Elevated erythrocyte sedimentation rate (ESR).
- ▶ Viral etiology. Antithyroid antibodies are absent or low, distinguishing it from autoimmune thyroiditis.

Infectious (suppurative) thyroiditis

- ▶ Severe, painful thyroid gland.
- ▶ Febrile with leukocytosis and elevated ESR.

IgG₄-related thyroiditis (Riedel thyroiditis)

- ▶ Most often in middle age or older women.
- ▶ Usually part of a systemic fibrosing syndrome.

General Considerations

Chronic lymphocytic thyroiditis, also known as “Hashimoto thyroiditis,” is the most common thyroid disorder in the United States. It predisposes to hypothyroidism. Cell-mediated autoimmunity is present with T-lymphocytes invading the thyroid gland, giving the microscopic appearance of “lymphocytic thyroiditis.” Humoral autoimmunity, with detectable serum antithyroid antibodies (TPO Ab or Tg Ab, or both), is present in most but not all affected patients. The humoral autoimmunity of autoimmune thyroiditis differs from that of Graves disease, where thyroid-stimulating immunoglobulins (TSI) bind to the TSH receptor in thyroid cell membranes and stimulate the gland to hyperfunction. The incidence of autoimmune thyroiditis varies by kindred, race, and sex. It is commonly familial. In the United States, elevated levels of antithyroid antibodies are found in 14.3% of Whites, 10.9% of Mexican Americans, and 5.3% of Blacks.

Childhood or occupational exposure to head-neck external beam radiation increases the lifetime risk of

Bryl M et al. The quality of life after transnasal microsurgical and endoscopic resection of nonfunctioning pituitary adenoma. *Adv Clin Exp Med*. 2020;29:921. [PMID: 32745380]

autoimmune thyroiditis. Women with gonadal dysgenesis (Turner syndrome) have a 15% incidence of thyroiditis by age 40 years. Thyroiditis is also commonly seen in patients with hepatitis C. Subclinical thyroiditis is extremely common; autopsy series have found focal thyroiditis in about 40% of women and 20% of men.

Dietary iodine supplementation (especially when excessive) increases the risk of autoimmune thyroiditis. Certain drugs can trigger autoimmune thyroiditis, including tyrosine kinase inhibitors, alemtuzumab, interferon-alpha, interleukin-2, thalidomide, lenalidomide, lithium, amiodarone, and immune checkpoint inhibitors.

Chronic hepatitis C is associated with an increased risk of autoimmune thyroiditis, with 21% of affected patients having antithyroid antibodies and 13% having hypothyroidism.

Autoimmune thyroiditis often progresses to hypothyroidism, which may be linked to thyrotropin receptor-blocking antibodies, detected in 10% of patients with autoimmune thyroiditis. Hypothyroidism is more likely to develop in persons who smoke cigarettes than in those who do not, possibly due to the thiocyanates in cigarette smoke. High serum levels of TPO Ab also predict progression from subclinical to symptomatic hypothyroidism. Although the hypothyroidism is usually permanent, up to 11% of patients experience a remission after several years. Hyperthyroidism can be caused by the destructive release of thyroid hormones (followed by hypothyroidism) or by increased synthesis of thyroid hormones (Graves disease).

Autoimmune thyroiditis is sometimes associated with other endocrine deficiencies as part of autoimmune polyendocrine syndrome type 2 (APS-II). Adults with APS-II are prone to autoimmune thyroiditis, type 1 diabetes mellitus, autoimmune gonadal failure, hypoparathyroidism, and adrenal insufficiency. Thyroiditis is frequently associated with other autoimmune conditions: pernicious anemia, Sjögren syndrome, vitiligo, inflammatory bowel disease, celiac disease, and gluten sensitivity.

Postpartum thyroiditis is an acute autoimmune thyroiditis that occurs soon after delivery in about 7% of women. The affected thyroid releases stored thyroid hormone, resulting in transient hyperthyroidism (often mild and undiagnosed), followed by hypothyroidism. The thyroid gland is not acutely tender, but some women complain of mild thyroid discomfort. Most women recover normal thyroid function. Women in whom postpartum thyroiditis develops have a 70% chance of recurrence after subsequent pregnancies. It occurs most commonly in women who have high levels of TPO Ab in the first trimester of pregnancy or immediately after delivery. It is also more common in women with preexistent type 1 diabetes mellitus, other autoimmunity, or a family history of autoimmune thyroiditis.

Painless (silent) sporadic subacute thyroiditis is a form of autoimmune thyroiditis that is similar to postpartum thyroiditis, except that it is not related to pregnancy. Causes include amiodarone and immunotherapy. Hyperthyroidism results from the release of stored thyroid hormone. This accounts for about 1% of cases of thyrotoxicosis and is followed by hypothyroidism that may or may not resolve spontaneously.

Painful subacute thyroiditis—also called de Quervain thyroiditis, granulomatous thyroiditis, and giant cell thyroiditis—is relatively common. Multinucleated giant cells are found on histology in the characteristically tender thyroid gland. Like painless subacute thyroiditis, most affected patients have transient hyperthyroidism, followed by hypothyroidism. Painful subacute thyroiditis is typically associated with a viral infection (including COVID-19) and often follows an upper respiratory tract infection. Some patients also have antithyroid antibodies. Its incidence peaks in the summer to early autumn. It affects both sexes, but young and middle-aged women are most commonly affected. Subacute thyroiditis can be a prominent sequelae of drug-induced hypersensitivity syndrome.

Infectious (suppurative) thyroiditis, a nonviral infection of the thyroid gland, is quite rare among immunocompetent patients, since the thyroid is resistant to infection due to its vasculature, encapsulation, and high iodine content. Congenital pyriform sinus fistulas are a cause for recurrent infectious thyroiditis. While infectious thyroiditis is usually bacterial, mycobacterial, fungal, and parasitic infections can occur, particularly in immunosuppressed individuals. In affected patients who are appropriately treated, when immunosuppression is reduced, the patient may experience an immune reconstitution inflammatory syndrome (IRIS) from residual antigens triggering the normal immune response.

IgG₄-related thyroiditis, also called Riedel thyroiditis, invasive fibrous thyroiditis, Riedel struma, woody thyroiditis, ligneous thyroiditis, and invasive thyroiditis, is the rarest form of thyroiditis. It is found most frequently in middle-aged or elderly women and is usually part of a multifocal systemic fibrosis syndrome. It may occur as a thyroid manifestation of IgG₄-related systemic disease.

► Clinical Findings

A. Symptoms and Signs

In **autoimmune thyroiditis**, the thyroid gland may be diffusely enlarged, firm, and finely nodular but is frequently not palpable. One thyroid lobe may be asymmetrically enlarged, raising concerns about neoplasm. Although patients may complain of neck tightness, pain and tenderness are not usually present. Other patients have no palpable goiter and no neck symptoms. The thyroid is fibrotic and atrophic in about 10% of cases, particularly in older women.

Symptoms and signs are mostly related to levels of thyroid hormone. Affected patients may have combinations of hyperthyroidism and hypothyroidism. For example, a patient with hypothyroidism might later develop hyperthyroidism that can wax and wane. Depression and chronic fatigue are more common, even after correction of hypothyroidism.

About one-third of patients have mild dry mouth (xerostomia) or dry eyes (keratoconjunctivitis sicca) related to Sjögren syndrome. Associated myasthenia gravis is usually of mild severity, mainly affecting the extraocular muscles and having a relatively low incidence of detectable AChR Ab or thymic disease. Associated celiac disease or gluten

intolerance can produce fatigue or depression, sometimes in the absence of gastrointestinal symptoms.

Postpartum thyroiditis is typically manifested by hyperthyroidism that begins 1–6 months after delivery and persists for only 1–2 months. Then, hypothyroidism tends to develop beginning 4–8 months after delivery.

In painless sporadic thyroiditis, thyrotoxic symptoms are usually mild; a small, nontender goiter may be palpated in about 50% of such patients. The course is similar to postpartum thyroiditis.

Painful subacute thyroiditis presents with an acute, usually painful enlargement of the thyroid gland, often with dysphagia. About 38% of patients have one thyroid lobe involved, while 62% have both lobes involved. Those with bilateral involvement are likely to be more hyperthyroid. The pain may radiate to the ears. Patients usually have a low-grade fever and fatigue. The manifestations may persist for weeks or months and may be associated with malaise. Thyrotoxicosis develops in 50% of affected patients and tends to last for several weeks. Subsequently, hypothyroidism develops that lasts 4–6 months. Normal thyroid function typically returns within 12 months, but persistent hypothyroidism develops in 5% of patients.

Infectious suppurative thyroiditis patients usually are febrile and have severe pain, tenderness, redness, and fluctuation in the region of the thyroid gland. In **IgG₄-related thyroiditis**, thyroid enlargement is often asymmetric; the gland is stony hard and adherent to the neck structures, causing signs of compression and invasion, including dysphagia, dyspnea, pain, and hoarseness. Related conditions include retroperitoneal fibrosis, fibrosing mediastinitis, sclerosing cervicitis, subretinal fibrosis, and sclerosing cholangitis.

B. Laboratory Findings

In **autoimmune thyroiditis** (including postpartum thyroiditis), there are usually increased circulating levels of the antithyroid antibodies TPO Ab (90%) or Tg Ab (40%). However, about 5% of patients with autoimmune thyroiditis have no detectable antithyroid antibodies. Most patients with thyroiditis caused by immune checkpoint inhibitors have no detectable antithyroid antibodies. Antithyroid antibodies decline during pregnancy and are often undetectable in the third trimester. Once autoimmune thyroiditis has been diagnosed, monitoring of these antibody levels is not helpful. The serum TSH level is elevated if thyroid hormone is inadequately released by the thyroid gland.

Patients with autoimmune thyroiditis have a 15% incidence of having serum antibodies (IgA tissue transglutaminase [tTG] antibody) and at least 5% have clinically significant celiac disease. Seronegative gluten sensitivity is even more common.

In **painful subacute thyroiditis**, the ESR is markedly elevated while antithyroid antibody titers are low, distinguishing it from autoimmune thyroiditis. In **infectious thyroiditis**, both the leukocyte count and ESR are usually elevated.

With hyperthyroidism due to autoimmune thyroiditis or painful subacute thyroiditis, serum FT₄ levels tend to be proportionally higher than T₃ levels, since the

hyperthyroidism is due to the passive release of stored thyroid hormone, which is predominantly T₄; this is in contrast to Graves disease and toxic nodular goiter, where T₃ is relatively more elevated. Because T₄ is less active than T₃, the hyperthyroidism seen in thyroiditis is usually less severe. Serum levels of TSH are suppressed in hyperthyroidism due to thyroiditis.

C. Imaging

In autoimmune thyroiditis, the ultrasound typically shows a gland with characteristic diffuse heterogeneous density and reduced echogenicity. It helps distinguish thyroiditis from multinodular goiter or thyroid nodules that are suspicious for malignancy. It is also helpful in guiding fine-needle aspiration (FNA) biopsy of small suspicious thyroid nodules. Color flow Doppler ultrasonography can help distinguish thyroiditis from Graves disease; in thyroiditis, vascularity is normal or reduced vascularity, whereas in Graves disease, the thyroid gland is hypervascular.

Radioiodine (RAI) uptake and scan can help distinguish thyroiditis from Graves disease; painful subacute thyroiditis exhibits a very low RAI uptake. However, RAI uptake may be normal or high with uneven uptake on the scan in chronic autoimmune thyroiditis (euthyroid or hypothyroid); CT or MRI is not useful in diagnosis.

[¹⁸F] Fluorodeoxyglucose positron emission tomography (¹⁸FDG-PET) scanning frequently shows diffuse thyroid uptake of isotope in cases of thyroiditis. In fact, of ¹⁸FDG-PET scans done for any reason, about 3% show such uptake. However, discrete thyroid nodules can also be discovered on ¹⁸FDG-PET scanning; these nodules are known as “thyroid PET incidentalomas” and 50% are malignant.

D. Fine-Needle Aspiration Biopsy

Patients with autoimmune thyroiditis who have a thyroid nodule should have an ultrasound-guided FNA biopsy, since the risk of papillary thyroid cancer is about 8% in such nodules. When infectious (suppurative) thyroiditis is suspected, an FNA biopsy with Gram stain and culture is required. FNA biopsy is usually not required for painful subacute thyroiditis but shows characteristic giant multinucleated cells.

► Complications

Autoimmune thyroiditis may lead to hypothyroidism. Hyperthyroidism may develop, either due to the emergence of Graves disease or due to the release of stored thyroid hormone, which is caused by inflammation. It is variably termed “hashitoxicosis” or “painless sporadic thyroiditis.” Euthyroid women with high serum TPO Ab may have an increased risk of miscarriage and preterm birth; unfortunately, treatment with levothyroxine fails to improve these risks. Perimenopausal women with high serum levels of TPO Ab have a higher relative risk of depression, independent of ambient thyroid hormone levels.

Subacute and chronic thyroiditis are complicated by the effects of pressure on the neck structures: dyspnea and, in Riedel struma, vocal cord palsy. Papillary thyroid

carcinoma or thyroid lymphoma may rarely be associated with chronic thyroiditis and must be considered in the diagnosis of uneven painless enlargements that continue despite treatment; such patients require FNA biopsy. In the suppurative forms of thyroiditis, any complication of infection may occur.

► Differential Diagnosis

All types of goiters must be considered in the differential diagnosis of thyroiditis, especially if enlargement is rapid. Unlike in goiters, in subacute thyroiditis there is very low RAI uptake and the T_4 and T_3 are elevated. Thyroid autoantibody tests have been helpful in the diagnosis of autoimmune thyroiditis, but the tests are not specific (positive in patients with multinodular goiters, malignancy [eg, thyroid carcinoma, lymphoma], and concurrent Graves disease). The subacute and suppurative forms of thyroiditis may resemble any infectious process in or near the neck structures. Chronic thyroiditis may resemble thyroid carcinoma, especially if the enlargement is uneven and if there is pressure on surrounding structures; both disorders may be present in the same gland.

► Treatment

A. Autoimmune Thyroiditis (Hashimoto)

If hypothyroidism is present, levothyroxine should be given in usual replacement doses (0.05–0.2 mg orally daily) (see Hypothyroidism & Myxedema, below). If hyperthyroidism is present, see Hyperthyroidism (Thyrotoxicosis), below.

In patients with a large goiter and normal or elevated serum TSH, an attempt is made to shrink the goiter with levothyroxine in doses sufficient to drive the serum TSH below the reference range while maintaining clinical euthyroidism. Suppressive doses of T_4 tend to shrink the goiter an average of 30% over 6 months. If the goiter does not regress, lower replacement doses of levothyroxine may be given. If the thyroid gland is only minimally enlarged and the patient is euthyroid, regular observation is indicated, since hypothyroidism may develop, often years later.

Dietary supplementation with selenium 200 mcg/day reduces serum levels of TPO Ab. In pregnant women with autoimmune thyroiditis, selenium supplementation at 83 mcg orally daily reduced the usual rebound postpartum increase in antithyroid antibodies without side effects on mother or newborn, but the clinical impact is not known.

B. Painful Subacute Thyroiditis

All treatment is empiric and must be continued for several weeks. Recurrence is common. The drug of choice is aspirin (325–650 mg orally every 4–6 hours, which relieves pain and inflammation) or NSAIDs. For patients with severe pain, prednisone, 20 mg orally daily for about 2 weeks, can be effective. Thyrotoxic symptoms are treated with propranolol, 10–40 mg orally every 6 hours, or propranolol ER, 60–160 mg orally daily. Iodinated contrast agents cause a prompt fall in serum T_3 levels and

a dramatic improvement in thyrotoxic symptoms. Iopodate sodium (Bilivist, Oragrafin) or iopanoic acid (Telepaque) is given orally in doses of 500 mg orally daily until serum FT_4 levels return to normal. Transient hypothyroidism is treated with T_4 (0.05–0.1 mg orally daily) if symptomatic.

C. Infectious (Suppurative) Thyroiditis

Treatment is with antibiotics and with surgical drainage when fluctuation is marked. Immunocompromised individuals are particularly at risk and coccidioidomycosis thyroiditis has been reported. Surgical thyroidectomy may be required.

D. IgG₄-Related Thyroiditis (Riedel Thyroiditis)

The treatment of choice is tamoxifen, 20 mg orally twice daily, which must be continued for years. Tamoxifen can induce partial to complete remissions in most patients within 3–6 months. Its mode of action appears to be unrelated to its antiestrogen activity. Short-term corticosteroid treatment may be added for partial alleviation of pain and compression symptoms. Surgical decompression usually fails to permanently alleviate compression symptoms; such surgery is difficult due to dense fibrous adhesions, making surgical complications more likely. Rituximab may be useful for Riedel thyroiditis that is refractory to tamoxifen and corticosteroids.

► Prognosis

Patients with autoimmune thyroiditis generally have an excellent prognosis, since the condition either remains stable for years or progresses slowly to hypothyroidism, which is easily treated. Autoimmune thyroiditis is occasionally associated with other autoimmune disorders (celiac disease, diabetes mellitus, Addison disease, pernicious anemia, etc). Although 80% of women with postpartum thyroiditis subsequently recover normal thyroid function, permanent hypothyroidism eventually develops in about 50% within 7 years, more commonly in women who are multiparous or who have had a spontaneous abortion. In subacute painful thyroiditis, spontaneous remissions and exacerbations are common; the disease process may smolder for months. Papillary thyroid carcinoma carries a relatively good prognosis when it occurs in patients with autoimmune thyroiditis.

Grani G et al. Contemporary thyroid nodule evaluation and management. *J Clin Endocrinol Metab*. 2020;105:2869. [PMID: 32491169]

Mantovani G et al. Selenium supplementation in the management of thyroid autoimmunity during pregnancy: results of the “SERENA study,” a randomized, double-blind, placebo-controlled trial. *Endocrine*. 2019;66:542. [PMID: 31129812]

Nguyen CT et al. Postpartum thyroiditis. *Clin Obstet Gynecol*. 2019;62:359. [PMID: 30844908]

Ragusa F et al. Hashimoto’s thyroiditis: Epidemiology, pathogenesis, clinic and therapy. *Best Pract Res Clin Endocrinol Metab*. 2019;33:101367. [PMID: 31812326]

HYPOTHYROIDISM & MYXEDEMA



ESSENTIALS OF DIAGNOSIS

- ▶ Autoimmune (Hashimoto) thyroiditis is the most common cause of hypothyroidism.
- ▶ Fatigue, cold intolerance, constipation, weight change, depression, menorrhagia, hoarseness.
- ▶ Dry skin, bradycardia, delayed return of deep tendon reflexes.
- ▶ FT_4 is usually low.
- ▶ TSH elevated in primary hypothyroidism.

► General Considerations

Hypothyroidism is common, affecting over 1% of the general population and about 5% of individuals over age 60 years. About 85% of affected individuals are women. Thyroid hormone deficiency affects almost all body functions. The degree of severity ranges from mild and unrecognized hypothyroid states to striking myxedema. Maternal hypothyroidism during pregnancy results in offspring with IQ scores that are an average 7 points lower than those of euthyroid mothers. Congenital hypothyroidism occurs in about 1:4000 births; untreated, it causes cretinism with permanent cognitive impairment.

Hypothyroidism may be due to failure or resection of the thyroid gland itself (primary hypothyroidism) or deficiency of pituitary TSH (secondary hypothyroidism). Autoimmune thyroiditis is the most common cause of hypothyroidism. A hypothyroid phase also occurs in subacute (de Quervain) viral thyroiditis following initial hyperthyroidism.

Goiter may be present with thyroiditis, iodide deficiency, genetic thyroid enzyme defects, food goitrogens in iodide-deficient areas (eg, turnips, cassavas), or, rarely, peripheral resistance to thyroid hormone or infiltrating diseases (eg, cancer, sarcoidosis). Goitrogenic medications include iodide, propylthiouracil (PTU) or methimazole, sulfonamides, amiodarone, interferon-alpha, interferon-beta, interleukin-2, and lithium. About 50% of patients taking lithium long term have an ultrasound-detectable goiter. Goiter is often absent in patients with autoimmune thyroiditis. Goiter is also usually absent when hypothyroidism is due to destruction of the gland by head-neck or chest-shoulder radiation therapy or ^{131}I therapy. Thyroidectomy causes hypothyroidism; after hemithyroidectomy, hypothyroidism develops in 22% of patients.

Amiodarone, because of its high iodine content, causes clinically significant hypothyroidism in about 15–20% of patients as well as thyrotoxicosis (see Amiodarone-induced thyrotoxicosis, below). Hypothyroidism occurs most often in patients with preexisting autoimmune thyroiditis. The T_4 level is low or low-normal, and the TSH is elevated, usually over 20 milli-international units/L. Another 17% of patients taking amiodarone are asymptomatic with normal

serum T_4 levels despite elevations in serum TSH; they can be closely monitored without levothyroxine therapy. Low-dose amiodarone is less likely to cause hypothyroidism. Patients with coronary artery disease who have amiodarone-induced symptomatic hypothyroidism are treated with just enough levothyroxine to relieve symptoms. Hypothyroidism usually resolves over several months if amiodarone is discontinued. Hypothyroidism may also develop in patients with a high iodine intake from other sources, especially if they have underlying lymphocytic thyroiditis. Some malignancies overexpress thyroid hormone inactivating enzyme (type 3 deiodinase) and cause “consumptive hypothyroidism.” This has occurred with large hemangiomas or a heavy tumor burden of colon cancer, basal cell cancer, fibrous tumors, or gastrointestinal stromal tumors (GISTs).

Chemotherapeutic agents that can cause silent thyroiditis include tyrosine kinase inhibitors, denileukin difitox, alemtuzumab, interferon-alpha, interleukin-2, thalidomide, lenalidomide, and immune checkpoint inhibitors (pembrolizumab, ipilimumab, tremelimumab, and atezolizumab). Thyroiditis usually starts with hyperthyroidism (often unrecognized) and then progresses to hypothyroidism. RAI-based targeted radioisotope therapy can also cause hypothyroidism.

► Clinical Findings

A. Symptoms and Signs

1. Common manifestations—Mild hypothyroidism often escapes detection without a screening serum TSH. Patients typically have nonspecific symptoms that include weight gain, fatigue, lethargy, depression, weakness, dyspnea on exertion, arthralgias or myalgias, muscle cramps, menorrhagia, constipation, dry skin, headache, paresthesias, cold intolerance, carpal tunnel syndrome, and Raynaud syndrome. Physical findings can include bradycardia; diastolic hypertension; thin, brittle nails; thinning of hair; peripheral edema; puffy face and eyelids; and skin pallor or yellowing (carotenemia). Delayed relaxation of deep tendon reflexes may be present. Patients often have a palpably enlarged thyroid (goiter) that arises due to elevated serum TSH levels or the underlying thyroid pathology.

2. Less common manifestations—Less common symptoms of hypothyroidism include diminished appetite and weight loss, hoarseness, decreased sense of taste and smell, and diminished auditory acuity. Some patients may complain of dysphagia or neck discomfort. Although most menstruating women have menorrhagia, some women have scant menses or amenorrhea. Physical findings may include loss of eyelash and eyebrow hairs; thickening of the tongue; hard pitting edema; and effusions into the pleural and peritoneal cavities as well as into joints. Galactorrhea may also be present. Cardiac enlargement (“myxedema heart”) and pericardial effusions may develop. Psychosis “myxedema madness” can occur from severe hypothyroidism or from toxicity of other drugs whose metabolism is slowed in hypothyroidism. Hypothermia and stupor or “myxedema coma,” which is

Table 26–2. Appropriate use of thyroid tests.

	Test	Comment
For screening	Serum thyroid-stimulating hormone (TSH)	Most sensitive test for primary hypothyroidism and hyperthyroidism
	Free thyroxine (FT_4)	Excellent test
For hypothyroidism	Serum TSH Thyroid peroxidase and thyroglobulin antibodies	High in primary and low in secondary hypothyroidism Elevated in autoimmune (Hashimoto) thyroiditis
For hyperthyroidism	Serum TSH	Suppressed except in TSH-secreting pituitary tumor or pituitary hyperplasia (rare)
	Triiodothyronine (T_3) or free triiodothyronine (FT_3) ^{123}I uptake and scan	Elevated Increased uptake; diffuse versus "hot" foci on scan
	Thyroid peroxidase and thyroglobulin antibodies Thyroid-stimulating immunoglobulin (TSI)	Elevated in Graves disease Usually (65%) positive in Graves disease
For thyroid nodules	Fine-needle aspiration (FNA) biopsy ^{123}I uptake and scan $^{99\text{m}}\text{Tc}$ scan Ultrasonography	Best diagnostic method for thyroid cancer Cancer is usually "cold"; less reliable than FNA biopsy Vascular versus less vascular Useful to assist FNA biopsy. Useful in assessing the risk of malignancy (multinodular goiter or pure cysts are less likely to be malignant). Useful to monitor nodules and patients after thyroid surgery for carcinoma.

often associated with infection (especially pneumonia), may develop in patients with severe hypothyroidism.

Some hypothyroid patients with autoimmune thyroiditis have symptoms that are not due to hypothyroidism but rather to conditions associated with autoimmune thyroiditis; these include Addison disease, hypoparathyroidism, diabetes mellitus, pernicious anemia, Sjögren syndrome, vitiligo, biliary cirrhosis, gluten sensitivity, and celiac disease.

B. Laboratory Findings

The single best screening test for hypothyroidism is the serum TSH (Table 26–2). In primary hypothyroidism, the serum TSH is increased in a reflex effort to stimulate the failing gland, while the serum FT_4 is low or low-normal. The normal reference range for ultrasensitive TSH levels is generally 0.4–4.0 milli-international units/L. The normal range of TSH varies with age; for example, the reference range for both children and elderly patients is higher than the reference range for younger patients.

Other laboratory abnormalities can include hypoglycemia or anemia (with normal or increased mean corpuscular volume). Hyponatremia due to the syndrome of inappropriate ADH secretion (SIADH) or decreased glomerular filtration rate is common. Additional frequent findings include increased serum levels of LDL cholesterol, triglycerides, lipoprotein (a), liver enzymes, creatine kinase, or PRL. Semen analysis shows an increase in abnormal sperm morphology. In patients with autoimmune thyroiditis, titers of antibodies against thyroperoxidase and thyroglobulin are high; serum antinuclear antibodies may be present but are not usually indicative of lupus.

Subclinical hypothyroidism is defined as the state of having a normal serum FT_4 with a serum TSH that is above the reference range. It occurs most often in persons aged 65 years or older, in whom the prevalence is 13%. Subclinical hypothyroidism is often transient and serum TSH levels normalize spontaneously in about 60% of cases within 5 years. The likelihood of TSH normalization is higher in patients without antithyroid antibodies and those with a marginally elevated serum TSH. The term "subclinical" is somewhat misleading, since it does not refer to patients' symptoms but rather refers only to serum hormone levels.

C. Imaging

Radiologic imaging is usually not necessary for patients with hypothyroidism. However, on CT or MRI, a goiter may be noted in the neck or in the mediastinum (retrosternal goiter). An enlarged thymus is frequently seen in cases of autoimmune thyroiditis. On MRI, the pituitary is often quite enlarged in primary hypothyroidism, due to hyperplasia of TSH-secreting cells.

► Differential Diagnosis

The differential diagnosis for subclinical hypothyroidism includes antibody interference with the serum TSH assay, macro-TSH, sleep deprivation, exercise, recovery from nonthyroidal illness, acute psychiatric emergencies, and other conditions and medications that can cause a low serum T_4 or high serum TSH in the absence of hypothyroidism (Table 26–3).

Euthyroid sick syndrome should be considered in patients without known thyroid disease who are found to have a low serum FT_4 with a serum TSH that is not elevated. This syndrome can be seen in patients with severe illness, caloric

Table 26–3. Factors that may cause aberrations in laboratory tests that may be mistaken for primary hypothyroidism.¹

Low Serum T ₄ or T ₃	High Serum TSH
Acute psychiatric illness	Acute psychiatric illness (transient) (14%)
Cirrhosis	Amiodarone
Familial thyroid-binding globulin deficiency	Anti-mouse antibodies
Laboratory error	Antithyrotropin antibodies
Nephrotic syndrome	Anti-TSH receptor antibodies
Severe illness	Autoimmune disease (assay interference)
Drugs	Drugs
Androgens	Amphetamines
Antiseizure drugs	Atypical antipsychotics
Carbamazepine	Dopamine agonists
Phenobarbital	Heroin
Phenytoin	Phenothiazines
Asparaginase	Elderly (especially women)
Carbamazepine (T ₄)	Exercise before testing
Chloral hydrate	Following prolonged primary hypothyroidism
Corticosteroids	Heterophile antibodies
Diclofenac (T ₃), naproxen (T ₃)	Laboratory error
Didanosine	Macro-thyrotropin
Fenclofenac	Nonadherence to thyroid replacement therapy
5-Fluorouracil	Pituitary TSH hypersecretion
Halofenate	Recovery from acute nonthyroidal illness (transient)
Imatinib	Strenuous exercise (acute)
Mitotane	Sleep deprivation (acute)
Nicotinic acid	TSH resistance
Oxcarbazepine	
Phenobarbital	
Phenytoin	
Salicylates in large doses (T ₃ and T ₄)	
Sertraline	
Stavudine	
T ₃ therapy (T ₄)	

¹True primary hypothyroidism may coexist.

T₄, levothyroxine; T₃, triiodothyronine; TSH, thyroid-stimulating hormone.

deprivation, or major surgery. Treatment with levothyroxine is not indicated for patients with euthyroid sick syndrome.

Serum TSH tends to be suppressed in severe nonthyroidal illness, making the diagnosis of concurrent primary hypothyroidism difficult, although the presence of a goiter suggests the diagnosis. The clinician must decide whether such severely ill patients (with a low serum T₄ but no elevated TSH) might have hypothyroidism due to hypopituitarism. Patients without symptoms of prior brain lesion or hypopituitarism are very unlikely to suddenly develop hypopituitarism during an unrelated illness. Patients with diabetes insipidus, hypopituitarism, or other signs of a central nervous system (CNS) lesion may be given T₄ empirically.

Patients receiving prolonged dopamine infusions can develop true secondary hypothyroidism caused by dopamine's direct suppression of TSH-secreting cells. Bexarotene and mitotane also cause secondary hypothyroidism in most patients.

Complications

Patients with severe hypothyroidism have an increased susceptibility to bacterial pneumonia. Megacolon has been described in long-standing hypothyroidism. Organic psychoses with paranoid delusions may occur ("myxedema madness"). Rarely, adrenal crisis may be precipitated by thyroid therapy. Rhabdomyolysis may occur and cause kidney dysfunction. Hypothyroidism is a rare cause of infertility, which may respond to thyroid replacement. Untreated hypothyroidism during pregnancy often results in miscarriage. Preexistent coronary artery disease and heart failure may be exacerbated by levothyroxine therapy.

Myxedema crisis refers to severe, life-threatening manifestations of hypothyroidism. Myxedema crisis particularly affects elderly women and can occur spontaneously in severely hypothyroid patients with prolonged exposure to the cold, with resultant hypothermia. It can also be induced by a stroke, heart failure, infection (particularly pneumonia), or trauma. Metabolism of drugs is slowed in hypothyroidism and myxedema crisis is often precipitated by the administration of sedatives, antidepressants, hypnotics, anesthetics, or opioids. The drugs further impair cognition and respiratory drive and can precipitate respiratory arrest. Affected patients have impaired cognition, ranging from confusion to somnolence to coma (myxedema coma). Convulsions and abnormal CNS signs may occur. Patients have profound hypothermia, hypoventilation, hyponatremia, hypoglycemia, hypoxemia, hypercapnia, and hypotension. Rhabdomyolysis and acute kidney injury may occur. The mortality rate is high.

Treatment

Before beginning therapy with thyroid hormone, the hypothyroid patient requires at least a clinical assessment for adrenal insufficiency and angina. The presence of either condition requires further evaluation and management.

Levothyroxine therapy is given to women attempting pregnancy, young adult patients aged 30 years or younger, patients with serum TSH levels 20 milli-international units/L or higher, and those with significant symptoms attributable to hypothyroidism. Other patients with subclinical hypothyroidism do not require levothyroxine therapy but must be monitored regularly for the emergence of symptoms.

A. Initial Treatment of Hypothyroidism

Synthetic levothyroxine is the preferred preparation for treating hypothyroidism. Intestinal absorption can vary by up to 15% with different oral levothyroxine preparations, so ideally, the patient should receive a consistent manufacturer's preparation. Lyophilized preparations of levothyroxine are available for reconstitution and intravenous administration, when indicated.

Otherwise healthy young and middle-aged adults with hypothyroidism may be treated initially with levothyroxine in average doses of about 1.6 mcg/kg/day. Lower doses can be used for very mild hypothyroidism, while full doses are

given for more symptomatic hypothyroidism. The initial hormonal goal of levothyroxine replacement therapy should be to normalize serum TSH levels. Bedtime levothyroxine administration results in somewhat higher serum T_4 and lower TSH levels than morning administration. Therefore, the administration timing for levothyroxine should be kept constant. After beginning daily administration, significant increases in serum T_4 levels are seen within 1–2 weeks, and near-peak levels are seen within 3–4 weeks.

Pregnant women with overt hypothyroidism or myxedema should be treated immediately with levothyroxine at full replacement doses (see Thyroiditis, Chapter 19).

Patients with stable coronary artery disease or those who are over age 60 years are treated with smaller initial doses of levothyroxine, 25–50 mcg orally daily; higher initial doses may be used if such patients are severely hypothyroid. The dose can be increased by 25 mcg every 1–3 weeks until the patient is euthyroid. Ideally, patients with hypothyroidism and unstable coronary artery disease or uncontrolled atrial fibrillation should begin levothyroxine replacement following medical or interventional therapy.

Myxedema crisis requires larger initial doses of levothyroxine intravenously, since myxedema itself can interfere with intestinal absorption of oral levothyroxine. Levothyroxine sodium 500 mcg is given intravenously as a loading dose, followed by 50–100 mcg intravenously daily; the lower dose is given to patients with suspected coronary artery disease. In patients with severe myxedema crisis, liothyronine (T_3 , Triostat) can be given intravenously with a loading bolus of 10–20 mcg, followed by 10 mcg intravenous boluses every 8–12 hours for the first 48 hours. The hypothermic patient is warmed only with blankets, since faster warming can precipitate cardiovascular collapse. Hypoglycemic patients are given 5% dextrose intravenously.

Hyponatremia in any hypothyroid patient requires evaluation for adrenal insufficiency. Medications and hypotonic intravenous solutions that can cause or aggravate hyponatremia are discontinued. Patients who are mildly symptomatic with a serum sodium 120–129 mEq/mL are treated with fluid restriction, unless they are dehydrated. Symptomatic patients with a serum sodium 120–129 mEq/mL must be managed as an inpatient and are administered 0.9% NaCl intravenously at 125 mL/h to correct hypovolemia. Hypothyroid patients with a serum sodium below 120 mEq/mL are treated with boluses of 100 mL of 3% NaCl intravenously with intravenous furosemide 20–40 mg to promote water diuresis; serum sodium levels must be monitored closely and boluses of 3% NaCl can be repeated about every 6 hours until the serum sodium rises to 120 mmol/L or higher. When giving intravenous saline to myxedematous patients, care must be taken to avoid fluid overload.

Patients with hypercapnia require mechanical assistance with ventilation. Opioid medications must be stopped or used in very low doses. Infections must be detected and treated aggressively. Patients in whom concomitant adrenal insufficiency is suspected are treated with hydrocortisone, 100 mg intravenously, followed by 25–50 mg every 6–8 hours.

B. Monitoring and Optimizing Treatment of Hypothyroidism

Regular clinical and laboratory monitoring is critical to determine the optimal levothyroxine dose for each patient. After initiating levothyroxine replacement, serum TSH, FT_4 , and FT_3 levels are monitored monthly, and the dose is adjusted with an aim to normalize the serum TSH within 2 months of commencing thyroid replacement therapy. The patient should be prescribed sufficient levothyroxine to restore a clinically euthyroid state; this can usually be attained by maintaining the serum TSH, FT_4 , and FT_3 within their reference ranges.

Pregnancy usually increases the levothyroxine dosage requirement; an increase in levothyroxine requirement has been noted as early as the fifth week of pregnancy (see Thyroid Disease, Chapter 19). Postpartum, levothyroxine replacement requirement ordinarily returns to prepregnancy level.

Decreased levothyroxine dose requirements occur in women after delivery, after bilateral oophorectomy or natural menopause, after cessation of oral estrogen replacement, or during therapy with GnRH agonists. Levothyroxine dosage may need to be titrated downward for patients who start taking teudiglutide for short bowel syndrome.

1. Elevated serum TSH level—For most patients, a high serum TSH indicates underreplacement with levothyroxine. However, patient nonadherence to prescribed levothyroxine is surprisingly common; before increasing the levothyroxine dosage, it is important to confirm patient compliance. For patients with coronary artery disease or recurrent atrial fibrillation, it may be prudent to administer lower doses of levothyroxine to keep serum TSH in the high-normal or even slightly elevated range.

Increased levothyroxine dosage requirements (low serum T_4 levels) can occur with drugs that increase the hepatic metabolism of levothyroxine (Table 26–3). Amiodarone can increase or decrease levothyroxine dose requirements. Malabsorption of levothyroxine can be caused by coadministration of binding substances, such as iron (eg, in multivitamins); fiber; raloxifene; sucralfate; aluminum hydroxide antacids; sevelamer; orlistat; bile acid-binding resins (cholestyramine and colestevexam); and calcium, magnesium, milk, coffee, and soy milk, or formula.

Proton pump inhibitors interfere slightly with the absorption of levothyroxine. Gastrointestinal disorders can interfere with levothyroxine absorption, including celiac disease, inflammatory bowel disease, lactose intolerance, *Helicobacter pylori* gastritis, and atrophic gastritis. Nephrotic syndrome can increase the required dose of oral levothyroxine. Women with hypothyroidism may require increased doses of levothyroxine after commencing oral estrogen therapy.

Serum TSH may be elevated transiently in acute psychiatric illness, with antipsychotics and phenothiazines, and during recovery from nonthyroidal illness. Autoimmune disease can interfere with the assay and cause false elevations of TSH.

2. Normal serum TSH level—For most patients, the goal of levothyroxine replacement is to maintain the serum TSH in the low normal range (0.4–2.0 milli-international

units/L). However, treated patients with normal serum TSH levels have higher serum LDL cholesterol levels, lower average basal metabolic rate, and lower serum T_3 levels compared to matched euthyroid controls. This appears to explain why some treated patients continue to have subjective symptoms suggestive of mild hypothyroidism, despite normal serum TSH levels. Such patients must be assessed for concurrent conditions, such as an adverse drug reaction, Addison disease, depression, hypogonadism, anemia, celiac disease, or gluten sensitivity. If such conditions are not present or are treated and hypothyroid-type symptoms persist, a serum T_3 or free T_3 level is often helpful. Low serum T_3 levels may reflect inadequate peripheral deiodinase activity to convert inactive T_4 to active T_3 . Unless contraindicated by unstable angina, such patients with continued hypothyroid-type symptoms may be carefully administered a slightly higher dose of levothyroxine to suppress the serum TSH while achieving clinical euthyroidism and a serum FT_3 near the low-normal range. For most patients with hypothyroidism, an ideal stable maintenance dose of levothyroxine can usually be found.

Desiccated natural porcine thyroid preparations containing both T_4 and T_3 (eg, Armour Thyroid, Nature-Throid, NP Thyroid) are prescribed by some clinicians. About 65 mg (1 grain) of desiccated thyroid is equivalent to 100 mcg of levothyroxine. Several professional medical societies discourage the use of desiccated thyroid preparations, but some patients prefer them.

3. Low or suppressed serum TSH level—A serum TSH level below the reference range (adults 0.4–4.0 milli-international units/L) is either “low” (0.1–0.39 milli-international units/L) or “suppressed” (less than 0.1 milli-international units/L). Clinically euthyroid patients receiving levothyroxine who have “low” TSH levels do not have increased morbidity. However, a “suppressed” serum TSH often indicates over-replacement with levothyroxine, and such patients may have symptoms of hyperthyroidism with an increased risk for atrial fibrillation, osteoporosis, and clinical hyperthyroidism. A suppressed serum TSH can occur with hypopituitarism, severe nonthyroidal illness, and some medications such as nonsteroidal anti-inflammatory drugs, biotin, opioids, nifedipine, verapamil, and high-dose (short-term) corticosteroids. Aside from the latter circumstances, when the serum TSH is suppressed, the dosage of levothyroxine is reduced. However, some patients feel unmistakably hypothyroid while taking the reduced dose of levothyroxine and have low serum T_3 or free T_3 levels. For such patients, a higher levothyroxine dose may be resumed with close surveillance for atrial fibrillation, osteoporosis, and manifestations of subtle hyperthyroidism.

► Prognosis

Patients with mild hypothyroidism caused by autoimmune thyroiditis have a remission rate of 11%. Hypothyroidism caused by interferon-alpha resolves within 17 months of stopping the drug in 50% of patients. With levothyroxine treatment of hypothyroidism, striking transformations take place both in appearance and mental function. Return

to a normal state is usually the rule, but relapses will occur if treatment is interrupted. Untreated patients with myxedema crisis have a mortality rate approaching 100%; even with optimal treatment, the mortality rate is 20–50%.

► When to Refer

- Difficulty titrating levothyroxine replacement to normal TSH or clinically euthyroid state.
- Any patient with significant coronary artery disease needing levothyroxine therapy.

► When to Admit

- Suspected myxedema crisis.
- Hypercapnia.

Bekkering GE et al. Thyroid hormones treatment for subclinical hypothyroidism: a clinical practice guideline. *BMJ*. 2019;365: l2006. [PMID: 31088853]

Biondi B et al. Subclinical hypothyroidism: a review. *JAMA*. 2019;322:153. [PMID: 31287527]

Burch HB. Drug effects on the thyroid. *N Engl J Med*. 2019;381:749. [PMID: 31433922]

McDermott MT. Hypothyroidism. *Ann Intern Med*. 2020;173: ITC1. [PMID: 32628881]

HYPERTHYROIDISM (Thyrotoxicosis)

ESSENTIALS OF DIAGNOSIS

- ▶ Sweating, weight loss or gain, anxiety, palpitations, loose stools, heat intolerance, menstrual irregularity.
- ▶ Tachycardia; warm, moist skin; stare; tremor.
- ▶ Graves disease: most common cause of hyperthyroidism; palpable goiter (sometimes with bruit) in most patients; ophthalmopathy also common.
- ▶ Amiodarone: most common cause of thyrotoxic crisis “thyroid storm.”
- ▶ Suppressed TSH in primary hyperthyroidism; usually increased T_4 , FT_4 , T_3 , FT_3 .

► General Considerations

The term “thyrotoxicosis” refers to the clinical manifestations associated with elevated serum levels of T_4 or T_3 that are excessive for the individual (hyperthyroidism).

A. Graves Disease

Graves disease (known as Basedow disease in Europe) is the most common cause of thyrotoxicosis. It is an autoimmune disorder, characterized by an increase in synthesis and release of thyroid hormones. Autoantibodies bind to the TSH receptors in the thyroid cell membranes and stimulate the gland to overproduce thyroid hormones.

These autoantibodies are known as thyroid-stimulating immunoglobulins (TSI) or thyrotropin receptor antibodies (TRAb). The presence of the latter antibodies distinguishes Graves disease from autoimmune chronic lymphocytic thyroiditis since in both conditions serum antithyroid antibodies (TPO Ab or Tg Ab or both) are usually present.

Graves disease is much more common in women than in men (8:1), and its onset is usually between the ages of 20 and 40 years. It may be accompanied by infiltrative ophthalmopathy (Graves exophthalmos) and, less commonly, by infiltrative dermopathy (pretibial myxedema). The thymus gland is typically enlarged and serum antinuclear antibody levels are usually elevated. Many patients with Graves disease have a family history of either Graves disease or autoimmune thyroiditis.

Dietary iodine supplementation can trigger Graves disease. Similarly, patients being treated with potassium iodide or amiodarone (which contains iodine) have an increased risk of developing Graves disease.

Chemotherapy with immune checkpoint inhibitors (ipilimumab, pembrolizumab, tremelimumab, and atezolizumab) and alemtuzumab (for multiple sclerosis) can both precipitate Graves disease and cause hyperthyroidism from destructive autoimmune thyroiditis (silent thyroiditis).

Patients with Graves disease have an increased risk of other systemic autoimmune disorders, including Sjögren syndrome, celiac disease, pernicious anemia, Addison disease, alopecia areata, vitiligo, type 1 diabetes mellitus, hypoparathyroidism, myasthenia gravis, and cardiomyopathy.

B. Toxic Multinodular Goiter and Thyroid Nodules

Autonomous hyperfunctioning thyroid nodules that produce hyperthyroidism are known as toxic multinodular goiter (Plummer disease) and are more prevalent among older adults and in iodine-deficient regions. A single hyperfunctioning nodule can also produce hyperthyroidism. Toxic multinodular goiter and Graves disease may sometimes coexist in the same gland (Marine-Lenhart syndrome). Thyroid cancer is found in about 4.7% of patients with toxic multinodular goiter.

C. Autoimmune (Postpartum or Silent) Thyroiditis and Subacute Thyroiditis

These conditions cause thyroid inflammation with release of stored hormone. They all produce a variable triphasic course: variable hyperthyroidism is followed by transient euthyroidism, and progresses to hypothyroidism (see Thyroiditis, above).

D. Medication-Induced Hyperthyroidism

1. Amiodarone-induced thyrotoxicosis—Amiodarone is 37% iodine by weight. The half-life of amiodarone and its metabolites is about 100 days. In the short term, amiodarone normally increases the serum TSH (without hypothyroidism), though usually not over 20 milli-international units/L. Serum T_4 and FT_4 rise about 40% and may become frankly elevated in clinically euthyroid patients. Meanwhile, serum T_3 levels decline. Due to these short-term changes, it is best to not check thyroid function tests during

the first 3 months of therapy with amiodarone, unless clinically indicated. After about 3 months, the serum TSH usually normalizes.

Amiodarone-induced thyrotoxicosis is diagnosed when serum TSH levels are suppressed and serum T_3 or FT_3 levels are high or high-normal. Amiodarone-induced thyrotoxicosis is categorized as type 1, type 2, or mixed (27%). Treatment is based on distinguishing type 1 from type 2. Type 1 is caused by the *active* production of excessive thyroid hormone. Type 2 is caused by thyroiditis with the *passive* release of stored thyroid hormone.

In the United States, amiodarone causes thyrotoxicosis in about 3% of patients taking the drug. In Europe and iodine-deficient geographic areas, amiodarone induces thyrotoxicosis in about 20%. Thyrotoxicosis can occur suddenly at any time during treatment and may even develop several months after it has been discontinued. Amiodarone is the leading cause for thyrotoxic crisis (“thyroid storm”); the manifestations can be missed since amiodarone tends to cause bradycardia. Therefore, thyroid function tests (TSH, FT_4 , T_3) should be checked before starting amiodarone, again at 3–6 months, and then at least every 6 months (sooner if clinically indicated).

2. Iodine-induced hyperthyroidism (Basedow disease)

The recommended iodine intake for nonpregnant adults is 150 mcg/day. Higher iodine intake can precipitate hyperthyroidism in patients with nodular goiters, autonomous thyroid nodules, or asymptomatic Graves disease, and less commonly in patients with no detectable underlying thyroid disorder. Common sources of excess iodine include intravenous iodinated radiocontrast dye, certain foods (eg, kelp, nori), topical iodinated antiseptics (eg, povidone iodine), and medications (eg, amiodarone or potassium iodide). Intravenous iodinated radiocontrast dye can rarely induce a painful, destructive subacute thyroiditis, similar to type 2 amiodarone-induced thyrotoxicosis.

3. Tyrosine kinase inhibitors—Silent autoimmune thyroiditis that releases stored thyroid hormone, resulting in hyperthyroidism, develops in about 3.2% of patients receiving chemotherapy with tyrosine kinase inhibitors (eg, axitinib, sorafenib, sunitinib). While such hyperthyroidism may be subclinical, thyrotoxic crisis has been reported. Hypothyroidism usually follows hyperthyroidism and overall occurs in 19% of patients taking these drugs.

4. Immune checkpoint inhibitor cancer therapy

Immune checkpoint inhibitor therapy directed against either PD-1/PD-L1 or CTLA-4/B7-1/B7-2 frequently precipitates autoimmune adverse reactions. Thyroid autoimmunity commonly causes thyroiditis, hypothyroidism (primary or secondary), or hyperthyroidism from either passive release of thyroid hormone or active production of thyroid hormone (Graves disease).

E. Pregnancy, hCG-Secreting Trophoblastic Tumors, and Testicular Choriocarcinoma

Human chorionic gonadotropin (hCG) can bind to the thyroid's TSH receptors. Very high levels of serum hCG, particularly during the first 4 months of pregnancy, may

cause sufficient receptor activation to cause gestational thyrotoxicosis. About 18% of pregnant women have a low serum TSH during pregnancy, but only about 0.2% of pregnant women have clinical hyperthyroidism that requires treatment. Pregnant women are more likely to have hCG-induced thyrotoxicosis if they have high levels of serum asialo-hCG, a subfraction of hCG that has a greater affinity for TSH receptors. Such women are also more likely to suffer from hyperemesis gravidarum. This condition must be distinguished from true Graves disease in pregnancy, which usually predates conception and may be associated with high serum levels of TSI and antithyroid antibodies or with exophthalmos.

High levels of hCG can also cause thyrotoxicosis in some cases of pregnancies with gestational trophoblastic disease (molar pregnancy, choriocarcinoma). Some such pregnancies have produced thyrotoxic crisis. Men have developed hyperthyroidism from high levels of serum hCG secreted by a testicular choriocarcinoma.

F. Rare Causes of Hyperthyroidism

Thyrotoxicosis factitia is due to intentional or accidental ingestion of excessive amounts of exogenous thyroid hormone. Struma ovarii is thyroid tissue contained in about 3% of ovarian dermoid tumors and teratomas. Pituitary TSH hypersecretion by a pituitary thyrotrophe tumor or hyperplasia can rarely cause hyperthyroidism; serum TSH is elevated or inappropriately normal in the presence of true thyrotoxicosis. Metastatic functioning thyroid carcinoma can cause hyperthyroidism in patients with a heavy tumor burden. Recombinant human thyroid-stimulating hormone (rhTSH) can rarely induce hyperthyroidism when it is given prior to RAI therapy or scanning for metastatic differentiated thyroid cancer.

► Clinical Findings

A. Symptoms and Signs

Thyrotoxicosis can produce nervousness, restlessness, heat intolerance, increased sweating, palpitations, pruritus, fatigue, muscle weakness, muscle cramps, frequent bowel movements, weight change (usually loss), or menstrual irregularities. There may be fine resting finger tremors, moist warm skin, fever, hyperreflexia, fine hair, and onycholysis. Angina or atrial fibrillation may also be present, sometimes in the absence of other thyrotoxic symptoms (apathetic hyperthyroidism). Women with postpartum thyroiditis are often asymptomatic or experience only minor symptoms, such as palpitations, heat intolerance, and irritability. Chronic thyrotoxicosis may cause osteoporosis. Even subclinical hyperthyroidism (suppressed serum TSH with normal FT₄) may increase the risk of nonvertebral fractures. Clubbing and swelling of the fingers (acropachy) develop rarely. Tetany is a rare presenting symptom; hyperthyroidism causes an increased renal excretion of magnesium, resulting in functional hypoparathyroidism and hypocalcemia.

Thyroid examination in patients with Graves disease usually reveals a diffusely enlarged thyroid, frequently asymmetric, often with a bruit. However, there may be no

palpable thyroid enlargement. The thyroid gland in painful subacute thyroiditis is usually moderately enlarged and tender. There is often dysphagia and pain that can radiate to the jaw or ear. In patients with toxic multinodular goiter, the thyroid usually has palpable nodules. Patients with silent thyroiditis or postpartum thyroiditis have either no palpable goiter or a small, nontender goiter.

Cardiopulmonary manifestations of thyrotoxicosis commonly include a forceful heartbeat, premature atrial contractions, and sinus tachycardia. Patients often have exertional dyspnea. Atrial fibrillation or atrial tachycardia occurs in about 8% of patients with thyrotoxicosis, more commonly in men, older adults, and those with ischemic or valvular heart disease. The ventricular response from the atrial fibrillation may be difficult to control. Thyrotoxicosis itself can cause a thyrotoxic cardiomyopathy, and the onset of atrial fibrillation can precipitate heart failure. Echocardiogram reveals pulmonary artery hypertension in about 40% of patients with hyperthyroidism. Even “subclinical hyperthyroidism” increases the risk for atrial fibrillation and overall mortality. Hemodynamic abnormalities and pulmonary hypertension are reversible with restoration of euthyroidism.

Thyrotoxic crisis or “thyroid storm” is an extreme form of severe thyrotoxicosis that is an immediate threat to life. Its manifestations are most often cardiac with heart failure, severe sinus tachycardia (60%), ventricular fibrillation (13%), frequent myocardial infarction, and cardiogenic shock; marked agitation or delirium (63%); high fever, vomiting, diarrhea, dehydration, and hepatic impairment (52%).

Eye manifestations that occur with hyperthyroidism are discussed in Thyroid Eye Disease, below.

Graves dermopathy (pretibial myxedema) occurs in about 3% of patients with Graves disease. It usually affects the pretibial region, but can also affect the dorsal forearms and wrists and dorsum of the feet. It is more common in patients with high levels of serum TSI and severe Graves ophthalmopathy. Glycosaminoglycans accumulation and lymphoid infiltration occur in affected skin, which becomes erythematous with a thickened, rough texture. Elephantiasis of the legs is a rare complication.

Thyroid acropachy is an extreme and unusual manifestation of Graves disease. It presents with digital clubbing, swelling of fingers and toes, and radiographic findings of periostitis involving phalangeal and metacarpal bones. Extremity skin can become very thickened, resembling elephantiasis. Thyroid acropachy is ordinarily associated with ophthalmopathy and thyroid dermopathy. Most affected patients are smokers.

Clinical hyperthyroidism during pregnancy has a prevalence of about 0.2%. It may commence before conception or emerge during pregnancy, particularly the first trimester. Pregnancy can have a beneficial effect on the thyrotoxicosis of Graves disease, with decreasing antibody titers and decreasing serum T₄ levels as the pregnancy advances; about 30% of affected women experience a remission by late in the second trimester. However, undiagnosed or undertreated hyperthyroidism in pregnancy carries an increased risk of miscarriage, preeclampsia-eclampsia, preterm delivery, abruptio placenta, maternal heart failure, and

thyrotoxic crisis (thyroid storm). Such thyrotoxic crisis can be precipitated by trauma, infection, surgery, or delivery and confers a fetal/maternal mortality rate of about 25%.

Hypokalemic periodic paralysis occurs in about 15% of Asian or Native American men with thyrotoxicosis and is 30 times more common in men than women. It is marked by sudden symmetric flaccid paralysis, along with hypokalemia and hypophosphatemia, that occurs during hyperthyroidism (often after intravenous dextrose, oral carbohydrates, or vigorous exercise) despite few, if any, of the classic signs of thyrotoxicosis. Attacks last 7–72 hours.

B. Laboratory Findings

Serum T_4 , T_3 , FT_4 , thyroid resin uptake, and FT_4 index are all usually increased. Sometimes the FT_4 level may be normal but with an elevated serum T_3 (T_3 toxicosis). The severity of the elevation of serum FT_4 and FT_3 levels does not always correlate with the severity of thyrotoxic manifestations; patients with thyrotoxic crisis tend to have serum thyroid levels that are not significantly higher than those with less pronounced symptoms. Serum T_4 or T_3 can be elevated in other nonthyroidal conditions (Table 26–4).

Table 26–4. Factors that can cause aberration laboratory tests for hyperthyroidism.

High Serum T_4 or T_3	Low Serum TSH
Laboratory error	Laboratory error
Collection vial contains gel barrier for T_3	African descent (3–4%)
Acute psychiatric problems (30%)	Autonomous thyroid or thyroid nodule
Acute or chronic active hepatitis, primary biliary cirrhosis	Corticosteroids (short-term use)
AIDS (increased TBG)	Drugs
Autoimmunity	Amphetamines
Euthyroid sick	Biotin supplements (certain assays)
Familial thyroid-binding abnormalities	Calcium channel blockers (nifedipine, verapamil)
Familial resistance to thyroid (Refetoff syndrome)	Dopamine
Pregnancy: morning sickness, hyperemesis gravidarum	Dopamine agonists
Drugs	Glucocorticoids
Amiodarone	Metformin
Amphetamines	Somatostatin analogs
Biotin supplements (certain assays)	Thyroid hormone
Clofibrate	Elderly euthyroid
Estrogens (oral)	hCG-secreting trophoblastic tumors
Heparin	Hypopituitarism
Heroin, methadone	Nonthyroidal illness (severe)
Perphenazine	Pregnancy (especially with morning sickness)
Tamoxifen	Suppression after recent therapy for hyperthyroidism
Thyroid hormone therapy (excessive or factitious)	TSH variants not detected by commercial assays

hCG, human chorionic gonadotropin; T_4 , levothyroxine; T_3 , triiodothyronine; TBG, thyroid-binding globulin; TSH, thyroid-stimulating hormone.

Serum TSH is suppressed in hyperthyroidism (except in the very rare cases of pituitary inappropriate secretion of thyrotropin). Serum TSH may be misleadingly low in other nonthyroidal conditions (Table 26–4). The term “**subclinical hyperthyroidism**” is used to describe individuals with a low serum TSH but normal serum levels of FT_4 and T_3 ; in such patients, the overall prevalence of symptomatic hyperthyroidism is 0.7–1.8% in iodine-sufficient patients and 2–15% in patients with iodine deficiency. About two-thirds of patients with subclinical hyperthyroidism have serum TSH levels of 0.1–0.4 milli-international units/L (mild subclinical hyperthyroidism), while the remainder have serum TSH levels below 0.1 milli-international units/L (severe subclinical hyperthyroidism).

Hyperthyroidism can cause hypercalcemia, increased liver enzymes, increased alkaline phosphatase, anemia, and neutropenia. Hyperthyroidism also increases urinary magnesium excretion, which can lead to hypomagnesemia, resulting in functional hypoparathyroidism with hypocalcemia. Hypokalemia and hypophosphatemia occur in thyrotoxic periodic paralysis.

Problems of diagnosis occur in patients with acute psychiatric disorders; about 30% of these patients have elevated serum T_4 levels without clinical thyrotoxicosis. The TSH is not usually suppressed, distinguishing psychiatric disorder from true hyperthyroidism. T_4 levels return to normal gradually.

In **Graves disease**, serum thyroid-stimulating immunoglobulin (TSI, TSHrAb) is usually detectable (65%). Very high serum TSI levels appear to predispose to Graves ophthalmopathy. TPO Ab or Tg Ab are usually elevated but are nonspecific. Serum antinuclear antibodies are also usually elevated without any evidence of SLE or other rheumatologic disease.

With painful **subacute thyroiditis**, patients often have an increased WBC, ESR, and C-reactive protein. About 25% have antithyroid antibodies (usually in low titer) and serum TSI (TSHrAb) levels are normal. Patients with iodine-induced hyperthyroidism have undetectable serum TSI (or TSHrAb), no serum TPO Ab, and an elevated urinary iodine concentration. In thyrotoxicosis factitia, serum thyroglobulin levels are low, distinguishing it from other causes of hyperthyroidism.

With **hyperthyroidism during pregnancy**, women have an elevated serum total T_4 and FT_4 while the TSH is suppressed. An apparent lack of full TSH suppression in hyperthyroidism can be seen due to misidentification of hCG as TSH in certain assays. The serum FT_4 assay is difficult to interpret in pregnancy. Although the serum T_4 is elevated in most pregnant women, values over 20 mcg/dL (257 nmol/L) are encountered only in hyperthyroidism. On treatment, serum total T_4 levels during pregnancy should be kept at about $1.5 \times$ the prepregnancy level. The T_3 resin uptake, which is low in normal pregnancy because of high thyroxine-binding globulin (TBG) concentration, is normal or high in thyrotoxic persons.

Since high levels of T_4 and FT_4 are normally seen in patients taking **amiodarone**, a suppressed TSH must be present along with a greatly elevated T_4 (greater than 20 mcg/dL [257 nmol/L]) or T_3 (greater than 200 ng/dL

[3.1 nmol/L]) in order to diagnose hyperthyroidism. In type 1 amiodarone-induced thyrotoxicosis, the presence of proptosis and serum TSI (TSHrAb) is diagnostic. In type 2 amiodarone-induced thyrotoxicosis, serum levels of interleukin-6 (IL-6) are usually quite elevated.

C. Radioisotope Uptake and Imaging

Note: All radioisotope testing is contraindicated during pregnancy or breastfeeding.

A high thyroid RAI uptake is seen in Graves disease and toxic nodular goiter. RAI scanning, however, is not necessary for diagnosis in patients with obvious Graves disease who have elevated serum TSI or associated Graves ophthalmopathy. A low RAI uptake is also characteristic of iodine-induced hyperthyroidism and thyroiditis (subacute, silent, or postpartum), distinguishing them from Graves disease. Patients with type 1 amiodarone-induced thyrotoxicosis have RAI uptake that is usually detectable, while in type 2 amiodarone-induced thyrotoxicosis, thyroid RAI uptake is usually below 3%. Women should ideally have the RAI scan extended to include the pelvis in order to screen for concomitant struma ovarii (rare).

Patients with Graves disease have increased or normal thyroid uptake of **technetium (Tc-99m) pertechnetate**, whereas those with thyrotoxicosis from thyroiditis (silent, subacute, postpartum) have reduced uptake. Technetium (Tc-99m) pertechnetate mimics RAI scanning but is more convenient, costs less, and confers less radiation exposure.

Thyroid ultrasound can be particularly helpful in hyperthyroid patients with palpable thyroid nodules. Thyroid ultrasound shows a variably heterogeneous, hypoechoic gland in thyroiditis. Color flow Doppler sonography is helpful to distinguish type 1 amiodarone-induced thyrotoxicosis (enlarged gland with normal to increased blood flow velocity and vascularity) from type 2 amiodarone-induced thyrotoxicosis (normal gland without increased vascularity).

99mTc-sestamibi scanning usually shows normal or increased uptake with type 1 amiodarone-induced thyrotoxicosis and decreased uptake in type 2.

MRI and CT scanning of the orbits are the imaging methods of choice to visualize Graves ophthalmopathy affecting the extraocular muscles. Imaging is required only in severe or unilateral cases or in euthyroid exophthalmos that must be distinguished from orbital pseudotumor, tumors, and other lesions.

Differential Diagnosis

True thyrotoxicosis must be distinguished from those conditions that elevate serum T_4 and T_3 or suppress serum TSH without affecting clinical status (see Table 26–4). Serum TSH is commonly suppressed in early pregnancy and only about 10% of pregnant women with a low TSH have clinical hyperthyroidism.

Some states of hypermetabolism without thyrotoxicosis—notably severe anemia, leukemia, polycythemia, cancer, and pheochromocytoma—rarely cause confusion. Acromegaly may also produce tachycardia, sweating, and thyroid enlargement.

The differential diagnosis for thyroid-associated ophthalmopathy includes an orbital tumor (eg, lymphoma) or pseudotumor. Ocular myasthenia gravis is another autoimmune condition that occurs more commonly in Graves disease but is usually mild, often with unilateral eye involvement. Acetylcholinesterase receptor antibody (AChR Ab) levels are elevated in only 36% of such patients, and a thymoma is present in 9%.

Diabetes mellitus and Addison disease may coexist with thyrotoxicosis and can aggravate the weight loss, fatigue, and muscle weakness seen with hyperthyroidism.

Complications

Hypercalcemia, osteoporosis, and nephrocalcinosis may occur in hyperthyroidism. Decreased libido, erectile dysfunction, diminished sperm motility, and gynecomastia may be noted in men. Other complications include cardiac arrhythmias and heart failure, thyroid crisis, ophthalmopathy, dermopathy, and thyrotoxic hypokalemic periodic paralysis.

Treatment

A. Treatment of Graves Disease

Table 26–5 outlines the treatment options for hyperthyroidism.

1. Propranolol—Propranolol is used for symptomatic relief of tachycardia, tremor, diaphoresis, and anxiety until the hyperthyroidism is resolved. It is the initial treatment of choice for thyrotoxic crisis and effectively treats thyrotoxic hypokalemic periodic paralysis. Treatment usually starts with propranolol ER every 12 hours for patients with severe hyperthyroidism due to accelerated metabolism of the propranolol; it may be given once daily as hyperthyroidism improves (Table 26–5).

2. Thiourea drugs—Methimazole or PTU is generally used for young adults or patients with mild thyrotoxicosis, small goiters, or fear of isotopes. See Treatment of Hyperthyroidism during Pregnancy-Planning, Pregnancy, and Lactation, below. Elderly patients usually respond particularly well. There is a 50% chance of remission of hyperthyroidism with long-term thiourea therapy. A better likelihood of long-term remission occurs in patients with small goiters, mild hyperthyroidism, those requiring small doses of thiourea, and those with serum TSI (TSHrAb) less than 2 milli-units/L. Patients whose TPO Ab and Tg Ab remain low after 2 years of therapy have been reported to have only a 10% rate of relapse. There should be no rush to discontinue thiourea therapy in favor of RAI or surgery, even after years of treatment. Thioureas may be continued long term for patients who are tolerating them well. The exception is women with thyrotoxic Graves disease who are planning pregnancy in the near future; thyroid surgery or RAI should be considered at least 4 months in advance of conception. Thiourea drugs are also useful for preparing nonpregnant hyperthyroid patients for surgery and elderly patients for RAI treatment.

All patients receiving thiourea therapy must be informed of the danger of agranulocytosis or pancytopenia and the need to stop the drug and seek medical attention

Table 26–5. Medications for the treatment of hyperthyroidism.¹

Medication	Dose and Frequency	Indications
Propranolol ER	Dose: 60–80 mg orally once daily, increasing every 3 days until heart rate < 90 beats per minute. Maximum dose: 320 mg daily	Symptomatic relief of tachycardia, tremor, diaphoresis, anxiety Thyrotoxic crisis Hypokalemic periodic paralysis
Thioureas Methimazole	Initial dose: usually 30–60 mg orally once daily Dose may be divided and given twice daily to avoid gastrointestinal upset Lower dose of 10–20 mg for very mild symptoms During pregnancy or breastfeeding, dose should not exceed 20 mg daily	Young adults Elderly patients Mild thyrotoxicosis Small goiter Fear of isotopes Precautions during pregnancy ²
Propylthiouracil (PTU)	Dose: 300–600 mg orally daily in four divided doses During pregnancy or breastfeeding, dose should not exceed 200 mg daily	Precautions during pregnancy ²
Iodinated contrast agents Iopanoic acid or ipodate sodium	Initial dose: 500 mg orally twice daily for 3 days Maintenance dose: 500 mg once daily	Effective temporary treatment of thyrotoxicosis, especially for patients who are very symptomatic Alternative treatment for patients intolerant of thioureas
Lithium carbonate	Dose: 500–750 mg orally daily in divided doses	Thioureas greatly preferred over lithium Alternative treatment of patients intolerant of thioureas Do not use during pregnancy
Radioactive iodine (RAI, ¹³¹ I)		Destroys overactive thyroid tissue See text for Precautions Avoid with thyroid eye disease (Graves ophthalmopathy)
Prednisone	Initial dose: 0.5–0.7 mg/kg orally daily After 2 weeks: begin to slowly taper and stop after about 3 months	Type 2 amiodarone-induced thyrotoxicosis

¹See text for expanded discussion of these agents.

²See Treatment of Hyperthyroidism During Pregnancy-Planning, Pregnancy, and Lactation in text.

immediately with the onset of any infection or unusual bleeding. Agranulocytosis (absolute neutrophil count below 500/mcL) or pancytopenia usually occurs abruptly in about 0.4% of patients taking either methimazole or PTU. Over 70% of agranulocytosis cases occur within the first 60 days and nearly 85% within 90 days of commencing therapy, but continued long-term vigilance for this side effect is required. About half the cases are discovered because of fever, pharyngitis, or bleeding, but the other cases are discovered with routine complete blood counts. There is a genetic tendency to develop agranulocytosis with thiourea therapy; if a close relative has had this adverse reaction, other therapies should be considered. Agranulocytosis generally remits spontaneously with discontinuation of the thiourea and during antibiotic treatment. Recovery has not been improved by filgrastim (granulocyte colony-stimulating factor). Surveillance of the WBC can be done when blood is drawn to check thyroid levels during the first few months of treatment. Such surveillance may be helpful, since some cases of agranulocytosis occur gradually and many cases may be discovered while the patient is still asymptomatic.

Other common side effects include pruritus, allergic dermatitis, nausea, and dyspepsia. Antihistamines may control mild pruritus without discontinuation of the drug. Since the two thiourea drugs are similar, patients who have a major allergic reaction to one should not be given the other.

The patient may become clinically hypothyroid for 2 weeks or more before TSH levels rise, the pituitary gland having been suppressed by the preceding hyperthyroidism. Therefore, the patient's changing thyroid status is best monitored clinically and with serum FT₄ levels. Rapid growth of a goiter usually occurs if prolonged hypothyroidism is allowed to develop; the goiter may sometimes become massive but usually regresses rapidly with reduction or cessation of thiourea therapy or with thyroid hormone replacement.

A. METHIMAZOLE—Except during the first trimester of pregnancy, methimazole is generally preferred over PTU, since methimazole is more convenient to use and is less likely to cause fulminant hepatic necrosis. Methimazole therapy is also less likely to cause ¹³¹I treatment failure. Methimazole may also be administered twice daily to reduce

the likelihood of gastrointestinal upset. Rare complications peculiar to methimazole include serum sickness, cholestatic jaundice, alopecia, nephrotic syndrome, hypoglycemia, and loss of taste. The dosage is reduced as manifestations of hyperthyroidism resolve and as the FT_4 level falls toward normal. Following ^{131}I therapy, the dose of methimazole is gradually reduced according to frequent thyroid function testing; most patients are able to discontinue methimazole within 1–3 months following RAI therapy.

B. PROPYLTHIOURACIL—Acute liver failure occurs in about 1 in 1000 patients, making PTU a second-line medication for treating patients with Graves hyperthyroidism. The onset of severe liver toxicity varies from 3 days to 12 months after starting PTU. Therefore, PTU is ordinarily reserved for treating women actively seeking fertility and during the first trimester of pregnancy, when it is preferred over methimazole. See Treatment of Hyperthyroidism During Pregnancy-Planning, Pregnancy, and Lactation, below. The dosage and frequency of administration are reduced as symptoms of hyperthyroidism resolve and the FT_4 level approaches normal. Other rare complications peculiar to PTU include arthritis, lupus, aplastic anemia, thrombocytopenia, and hypoprothrombinemia. With PTU, acute hepatitis occurs rarely and is treated with prednisone.

3. Iodinated contrast agents—Iopanoic acid (Telepaque) and ipodate sodium (Bilivist, Oragrafin) are iodinated contrast agents that provide effective temporary treatment for thyrotoxicosis of any cause and are particularly useful for patients who are symptomatically very thyrotoxic. These agents inhibit peripheral 5'-monodeiodination of T_4 , thereby blocking its conversion to active T_3 . Within 24 hours, serum T_3 levels fall an average of 62%. For patients with **Graves disease**, methimazole is begun first to block iodine organification; the next day, ipodate sodium or iopanoic acid may be added. They offer a therapeutic option for patients with subacute thyroiditis, amiodarone-induced thyrotoxicosis, T_4 overdosage, and for those intolerant to thioureas. Treatment periods of 8 months or more are possible, but efficacy tends to wane with time. In Graves disease, thyroid RAI uptake may be suppressed during treatment but typically returns to pretreatment uptake by 7 days after discontinuation of the drug, allowing ^{131}I treatment.

4. Lithium carbonate—Thioureas are greatly preferred over lithium for the medical treatment of hyperthyroidism in Graves disease. However, lithium may be used effectively in cases of methimazole or PTU-induced hepatic toxicity or leukopenia. Lithium should not be used during pregnancy. Most patients require concurrent treatment with propranolol and sometimes prednisone.

5. Radioactive iodine (RAI, ^{131}I)— ^{131}I therapy destroys overactive thyroid tissue (either diffuse or toxic nodular goiter). Adolescent and adult patients who have been treated with ^{131}I in adulthood do not have an increased risk of subsequent thyroid cancer or leukemia. However, conflicting evidence has shown either no increased risk or a slightly increased risk for subsequent solid tumor malignancies following ^{131}I treatment for hyperthyroidism. Children born to

parents previously treated with ^{131}I show no increase in rates of congenital abnormalities.

Precautions: Because radiation is harmful to the fetus and children, *RAI should not be given to pregnant or lactating women or to mothers who lack childcare. Women are advised to avoid pregnancy for at least 4 months following ^{131}I therapy. A pregnancy test should be obtained within 48 hours before therapy for any woman with childbearing potential. Men have been found to have abnormal spermatozoa for up to 6 months following ^{131}I therapy and are advised to use contraceptive methods during that time.*

Patients may receive ^{131}I while being symptomatically treated with propranolol ER, which is then reduced in dosage as hyperthyroidism resolves. A higher rate of ^{131}I treatment failure has been reported in patients with Graves disease who have been receiving methimazole or PTU. However, therapy with ^{131}I will usually be effective if the methimazole is discontinued at least 3–4 days before RAI therapy and if the therapeutic dosage of ^{131}I is adjusted (upward) according to RAI uptake on the pretherapy scan. Prior to ^{131}I therapy, patients are instructed against receiving intravenous iodinated contrast and should consume a low-iodine diet.

The presence of Graves ophthalmopathy is a relative contraindication to ^{131}I therapy. Following ^{131}I treatment for hyperthyroidism, Graves ophthalmopathy appears or worsens in 15% of patients (23% in cigarette smokers and 6% in non-smokers) and improves in none. Among patients receiving prednisone following ^{131}I treatment, preexistent ophthalmopathy worsens in none and improves in 67%. Therefore, patients with Graves ophthalmopathy who are to be treated with ^{131}I should be considered for prophylactic prednisone (20–40 mg orally daily) for 2 months following administration of ^{131}I , particularly in patients who have severe orbital involvement.

Cigarette use increases the risk of having a flare in ophthalmopathy following ^{131}I treatment and also reduces the effectiveness of prednisone treatment. Patients who smoke cigarettes are strongly encouraged to quit prior to ^{131}I treatment. Smokers receiving ^{131}I should be considered for prophylactic prednisone.

FT_4 levels may sometimes drop within 2 months after ^{131}I treatment, but then rise again to thyrotoxic levels, at which time thyroid RAI uptake is low. This phenomenon is caused by a release of stored thyroid hormone from injured thyroid cells and does not indicate a treatment failure. In fact, serum FT_4 then falls abruptly to hypothyroid levels.

There is a high incidence of hypothyroidism in the months to years after ^{131}I , even when low activities are given. Patients with Graves disease treated with ^{131}I also have an increased lifetime risk of developing hyperparathyroidism, particularly when ^{131}I therapy was administered in childhood or adolescence. Lifelong clinical follow-up is mandatory, with measurements of serum TSH, FT_4 , and calcium when indicated.

6. Thyroid surgery—Surgery may be indicated for patients with Graves disease who are intolerant to thioureas, women planning pregnancy in the near future, patients who choose not to have RAI therapy, and patients with Graves ophthalmopathy. The surgical procedure of choice is a total resection of one lobe and a subtotal resection of the other lobe,

leaving about 4 g of thyroid tissue (Hartley–Dunhill operation). Total thyroidectomy of both lobes poses an increased risk of hypoparathyroidism and damage to the recurrent laryngeal nerves. See below for surgical treatment of Graves disease during pregnancy.

Patients are ordinarily rendered euthyroid preoperatively with a thiourea drug (Table 26–5). Propranolol ER is given until the heart rate is less than 90 beats per minute and continued until the serum T_3 (or free T_3) is normal preoperatively. If a patient undergoes surgery while thyrotoxic, larger doses of propranolol are given perioperatively to reduce the likelihood of thyroid crisis. Ipodate sodium or iopanoic acid may be used in addition to a thiourea to accelerate the decline in serum T_3 . The patient should be euthyroid by the time of surgery.

To reduce thyroid vascularity preoperatively, the patient may be treated for 3–10 days preoperatively with oral potassium iodide 25–50 mg (eg, ThyroShield 65 mg/mL, 0.5 mL, or SSKI 1 g/mL, 1 drop) three times daily. However, preoperative potassium iodide often increases the volume of the thyroid, so the requirement for preoperative potassium iodide for Graves disease is debatable. Preoperative iodide supplementation is not recommended prior to surgery for multinodular goiter. Alternatively, iodinated radiocontrast agents (eg, iopanoic acid) may be given for 1 week preoperatively.

Surgical morbidity includes damage to a recurrent laryngeal nerve, with resultant vocal cord paralysis. If both recurrent laryngeal nerves are damaged, airway obstruction may develop, and the patient may require intubation and tracheostomy. Hypoparathyroidism also occurs; serum calcium levels must be checked postoperatively. Patients should be admitted for thyroidectomy surgery for at least an overnight observation period.

B. Treatment of Toxic Solitary Thyroid Nodules

Toxic solitary thyroid nodules are usually benign but may rarely be malignant. If a nonsurgical therapy is elected, the nodule should be evaluated with a fine-needle aspiration (FNA) biopsy. **Medical therapy** for hyperthyroidism caused by a single hyperfunctioning thyroid nodule may be treated symptomatically with propranolol ER and methimazole or PTU, as in Graves disease (Table 26–5). Patients who tolerate methimazole well may elect to continue it for long-term therapy. The dose of methimazole should be adjusted to keep the TSH slightly suppressed, so the risk of TSH-stimulated growth of the nodule is reduced. **Surgical treatment** is usually recommended for patients under age 40 years, for healthy older patients with toxic solitary thyroid nodules, and for nodules that are suspicious for malignancy. Patients are made euthyroid with a thiourea preoperatively and given several days of iodine, ipodate sodium, or iopanoic acid before surgery. Postoperative hypothyroidism usually resolves spontaneously, but permanent hypothyroidism occurs in about 14% of patients by 6 years after surgery. ^{131}I therapy may be offered to patients with a toxic solitary nodule who are over age 40 or in poor health (see **Precautions** for RAI use, above). RAI should not be given to women with Graves disease within 3 months prior to a planned conception. If the patient has been

receiving methimazole preparatory to ^{131}I , the TSH should be kept slightly suppressed in order to reduce the uptake of ^{131}I by the normal thyroid. Nevertheless, permanent hypothyroidism occurs in about one-third of patients by 8 years after ^{131}I therapy. The nodule remains palpable in 50% and may grow in 10% of patients after ^{131}I .

C. Treatment of Toxic Nodular Goiter

Medical therapy for patients with toxic nodular goiter consists of propranolol ER (while hyperthyroid) and a thiourea, as in Graves disease (Table 26–5). Thioureas (methimazole or PTU) reverse hyperthyroidism but do not shrink the goiter. There is a 95% recurrence rate if the drug is stopped.

Surgical therapy is the definitive treatment for a large toxic nodular goiter, following therapy with a thiourea to render them euthyroid. Surgery is particularly indicated to relieve pressure symptoms or for cosmetic indications. Patients with toxic nodular goiter are not treated preoperatively with potassium iodide. Total or near-total thyroidectomy is recommended, since surgical pathology reveals unsuspected differentiated thyroid cancer in 18.3% of cases.

^{131}I therapy may be used to treat patients with toxic nodular goiter. See **Precautions** for RAI use, above. Any suspicious nodules should be evaluated beforehand for malignancy with FNA cytology. Patients are rendered euthyroid with methimazole, which is stopped 3–4 days before a repeat ^{131}I therapy.

Meanwhile, the patient follows a low-iodine diet in order to enhance the thyroid gland's uptake of ^{131}I , which may be relatively low in this condition (compared to Graves disease). Relatively high doses of ^{131}I are usually required; hypothyroidism or recurrent thyrotoxicosis typically occurs, so patients must be monitored closely. Peculiarly, in about 5% of patients with diffusely nodular toxic goiter, the administration of ^{131}I therapy may induce Graves disease. Also, Graves ophthalmopathy has occurred rarely following ^{131}I therapy for multinodular goiter.

D. Treatment of Hyperthyroidism from Thyroiditis

Patients with thyroiditis (subacute, postpartum, or silent) are treated with propranolol during the hyperthyroid phase, which usually subsides spontaneously within weeks to months. For symptomatic relief, begin propranolol ER until the heart rate is less than 90 beats per minute (Table 26–5). Ipodate sodium or iopanoic acid, 500 mg orally daily, promptly corrects elevated T_3 levels and is continued for 15–60 days until the serum FT_4 level normalizes. Thioureas are ineffective, since thyroid hormone production is actually low in this condition. Patients are monitored carefully for the development of hypothyroidism and treated with levothyroxine as needed. With subacute thyroiditis, pain can usually be managed with NSAIDs and corticosteroids, but opioid analgesics are sometimes required.

E. Treatment of Hyperthyroidism During Pregnancy-Planning, Pregnancy, and Lactation

Due to the increased risk of congenital anomalies with every thiourea, all women who are planning to become pregnant are encouraged to consider definitive therapy

with ^{131}I or surgery well before conception. Both men and women who are planning pregnancy should not have ^{131}I treatment within about 4 months of conception. See **Precautions** for RAI use, above. Dietary iodine must not be restricted for such women to protect the fetus from iodine deficiency.

First-trimester fetal exposure to thioureas (methimazole or PTU) increases the risk of birth defects by about 2%. The fetal anomalies associated with PTU are typically less severe than those associated with methimazole; therefore, PTU is the preferred thiourea for women actively seeking fertility and during the first trimester of pregnancy, despite the very low risk for hepatic necrosis with PTU. Therefore, women should be treated with PTU immediately prepregnancy and through the first trimester; during pregnancy, the dose of PTU is kept below 200 mg daily to avoid goitrous hypothyroidism in the infant. PTU can be switched to methimazole in the second trimester (see **Thiourea drugs**, above). Thiourea should be given in the smallest dose possible, permitting mild subclinical hyperthyroidism to occur, since it is usually well tolerated. About 30% of women with Graves disease experience a remission by the late second trimester.

Both PTU and methimazole cross the placenta and can induce hypothyroidism, with fetal TSH hypersecretion and goiter. Fetal ultrasound at 20–32 weeks' gestation can visualize any fetal goiter, allowing fetal thyroid dysfunction to be diagnosed and treated. Thyroid hormone administration to the mother does not prevent hypothyroidism in the fetus, since T_4 and T_3 do not freely cross the placenta. Fetal hypothyroidism is rare if the mother's hyperthyroidism is controlled with small daily doses of PTU (50–150 mg/day orally) or methimazole (5–15 mg/day orally). Serum total T_4 levels during pregnancy should be kept at about $1.5 \times$ the prepregnancy level. Maternal serum TSI levels over 500% at term predict an increased risk of neonatal Graves disease in the infant.

Subtotal thyroidectomy is indicated for pregnant women with Graves disease or for fertile women of reproductive age who are sexually active and decline contraceptives, under the following circumstances: (1) severe adverse reaction to thioureas; (2) high dosage requirement for thioureas (methimazole greater than or equal to 30 mg/day or PTU greater than or equal to 450 mg/day); or (3) uncontrolled hyperthyroidism due to nonadherence to thiourea therapy. Surgery is best performed during the second trimester.

Both methimazole and PTU are secreted in breast milk but not in amounts that affect the infant's thyroid hormone levels. No adverse reactions to these drugs have been reported in breast-fed infants. See Table 26–5 for recommended doses. It is recommended that the medication be taken just after breastfeeding.

F. Treatment of Amiodarone-Induced Thyrotoxicosis

Patients with either type 1 or type 2 amiodarone-induced thyrotoxicosis require treatment with propranolol ER for symptomatic relief and methimazole (Table 26–5). After two doses of methimazole, iopanoic acid or sodium

ipodate may be added to the regimen to further block conversion of T_4 to T_3 until the thyrotoxicosis is resolved. If iopanoic acid or sodium ipodate is not available, the alternative is potassium perchlorate; it is given in doses of less than or equal to 1000 mg daily (in divided doses) for a course not to exceed 30 days in order to avoid the complication of aplastic anemia. Amiodarone may be withdrawn but this does not have a significant therapeutic impact for several months because of its long half-life. For patients with type 1 amiodarone-induced thyrotoxicosis, therapy with ^{131}I may be successful, but only for those with sufficient RAI uptake. Patients with clear-cut type 2 amiodarone-induced thyrotoxicosis are usually also treated with prednisone for about 2 weeks and then slowly tapered and finally withdrawn after about 3 months. Subtotal thyroidectomy should be considered for patients with amiodarone-induced thyrotoxicosis that is resistant to treatment.

G. Treatment of Complications

1. Thyroid eye disease—See Thyroid Eye Disease (Graves Ophthalmopathy below).

2. Cardiac complications—

A. SINUS TACHYCARDIA—Treatment consists of treating the thyrotoxicosis. A beta-blocker such as propranolol is used in the interim unless there is an associated cardiomyopathy.

B. ATRIAL FIBRILLATION—Hyperthyroidism must be treated immediately. Other drugs, including digoxin, beta-blockers, and anticoagulants, may be required. Electrical cardioversion is unlikely to convert atrial fibrillation to normal sinus rhythm while the patient is thyrotoxic. Spontaneous conversion to normal sinus rhythm occurs in 62% of patients with return of euthyroidism, but that likelihood decreases with age. Following conversion to euthyroidism, there is a 60% chance that atrial fibrillation will recur, despite normal thyroid function tests. Those with persistent atrial fibrillation may have elective cardioversion following anticoagulation 4 months after resolution of hyperthyroidism.

(1) Digoxin—Digoxin is used to slow a rapid ventricular response to thyrotoxic atrial fibrillation; it must be used in larger than normal doses. Digoxin doses are reduced as hyperthyroidism is corrected.

(2) Beta-blockers—Beta-blockers may also reduce the ventricular rate, but they must be used with caution, particularly in patients with heart failure with reduced ejection fraction. An initial trial of a short-duration beta-blocker should be considered, such as esmolol intravenously. If a beta-blocker is used, doses of digoxin must be reduced.

(3) Anticoagulants—Dabigatran malabsorption has been reported in thyrotoxicosis-induced diarrhea. The doses of warfarin required in thyrotoxicosis are smaller than normal because of an accelerated plasma clearance of vitamin K-dependent clotting factors. Higher warfarin doses are usually required as hyperthyroidism subsides.

C. HEART FAILURE—Thyrotoxicosis can cause high-output heart failure due to extreme tachycardia, cardiomyopathy, or both. Aggressive treatment of the hyperthyroidism is required in either case.

Heart failure may also occur as a result of low-output dilated cardiomyopathy. It is uncommon and may be caused by an idiosyncratic severe toxic effect of hyperthyroidism upon certain hearts. Cardiomyopathy may occur at any age and without preexisting cardiac disease. See Chapter 10 for treatment of heart failure and dilated cardiomyopathy. The patient should be rendered euthyroid. However, the heart failure usually persists despite correction of the hyperthyroidism.

D. APATHETIC HYPERTHYROIDISM—Apathetic hyperthyroidism may present with angina pectoris. Treatment is directed at reversing the hyperthyroidism as well as providing standard antianginal therapy. PCI or CABG can often be avoided by prompt diagnosis and treatment.

3. Thyrotoxic crisis or “thyroid storm”—Intensive care unit admission is required. A thiourea drug is given (eg, methimazole, 15–25 mg orally every 6 hours, or PTU, 150–250 mg orally every 6 hours). Iopodate sodium (500 mg/day orally) can be helpful if begun 1 hour *after* the first dose of thiourea. Iodide is given 1 hour later as potassium iodide (10 drops three times daily orally). Propranolol is given in a dosage of 0.5–2 mg intravenously every 4 hours or 20–120 mg orally every 6 hours. Hydrocortisone is usually given in doses of 50 mg orally every 6 hours, with rapid dosage reduction as the clinical situation improves. Plasmapheresis has been successfully used in refractory cases to directly remove thyroid hormone. Aspirin is avoided since it displaces T₄ from thyroxine-binding globulin (TBG), raising FT₄ serum levels. For refractory cases, emergency surgical thyroidectomy is an option.

Supportive care is usually required, including vasopressors, mechanical ventilation, dialysis, and extracorporeal membrane oxygenation (ECMO) for cardiogenic shock.

4. Hyperthyroidism from postpartum thyroiditis—Propranolol ER is given during the hyperthyroid phase followed by levothyroxine during the hypothyroidism phase.

5. Graves dermopathy—Treatment involves application of a topical corticosteroid (eg, fluocinolone) with nocturnal plastic occlusive dressings. Compression stockings may improve any associated edema.

6. Thyrotoxic hypokalemic periodic paralysis—Therapy with oral propranolol, 3 mg/kg in divided doses, normalizes the serum potassium and phosphate levels and reverses the paralysis within 2–3 hours. No intravenous potassium or phosphate is usually required. Intravenous dextrose and oral carbohydrate aggravate the condition and are to be avoided. Therapy is continued with propranolol, 60–80 mg orally every 8 hours (or propranolol ER daily at equivalent daily dosage), along with a thiourea drug (eg, methimazole) to treat the hyperthyroidism.

7. Thyroid acropachy—This rare complication of Graves disease is often mild and may not require therapy. More severe cases are treated with systemic immunosuppressant

therapy that may include intravenous immune globulin and rituximab.

► Prognosis

Mild **Graves disease** may sometimes subside spontaneously. Graves disease that presents in early pregnancy has a 30% chance of spontaneous remission before the third trimester. The ocular, cardiac, and psychological complications can become serious and persistent even after treatment. Permanent hypoparathyroidism and vocal cord palsy are risks of surgical thyroidectomy. Recurrences are common following thiourea therapy but also occur after low-dose ¹³¹I therapy or subtotal thyroidectomy. With adequate treatment and long-term follow-up, the results are usually good. However, despite treatment for hyperthyroidism, women experience an increased long-term risk of death from thyroid disease, cardiovascular disease, stroke, and fracture of the femur. Posttreatment hypothyroidism is common. It may occur within a few months or up to several years after RAI therapy or subtotal thyroidectomy. Patients with thyrotoxic crisis have a high mortality rate despite treatment.

Subclinical hyperthyroidism generally subsides spontaneously. Progression to symptomatic thyrotoxicosis occurs at a rate of 1–2% per year in patients without a goiter and at a rate of 5% per year in patients with a multinodular goiter. Most patients do well without treatment and the serum TSH usually reverts to normal within 2 years. Most such patients do not have accelerated bone loss. However, if a baseline bone density shows significant osteopenia, bone densitometry may be performed periodically. In persons over age 60 years, serum TSH is suppressed (below 0.1 milli-international units/L) in 3% and mildly low (0.1–0.4 milli-international units/L) in 9%. The chance of developing atrial fibrillation is 2.8% yearly in elderly patients with a suppressed TSH and 1.1% yearly in those with mildly low TSH. Asymptomatic persons with very low serum TSH are monitored closely but are not treated unless atrial fibrillation or other manifestations of hyperthyroidism develop.

► When to Admit

- Thyroid crisis.
- Hyperthyroidism-induced atrial fibrillation with severe tachycardia.
- Thyroidectomy.

Biondi B et al. Subclinical hyperthyroidism. N Engl J Med. 2018; 378:2411. [PMID: 29924956]

Bourcier S et al. Thyroid storm in the ICU: a retrospective multicenter study. Crit Care Med. 2020;48:83. [PMID: 31714398]

Gronich N et al. Cancer risk after radioactive iodine treatment for hyperthyroidism: a cohort study. Thyroid. 2020;30:243. [PMID: 31880205]

McDermott MT. Hyperthyroidism. Ann Intern Med. 2020; 172:ITC49 [PMID: 32252086]

Yu W et al. Side effects of PTU and MMI in the treatment of hyperthyroidism: a systematic review and meta-analysis. Endocr Pract. 2020;26:207. [PMID: 31652102]

THYROID EYE DISEASE

► General Considerations

Thyroid eye disease (Graves ophthalmopathy) is a syndrome of clinical and orbital imaging abnormalities caused by deposition of mucopolysaccharides and infiltration with chronic inflammatory cells of the orbital tissues, particularly the extraocular muscles. In patients with Graves disease, 20–40% have clinically apparent eye disease; about 5–10% of patients experience severe exophthalmos. The severity of eye disease is not closely correlated with the severity of thyrotoxicosis; clinical or laboratory evidence of thyroid dysfunction and thyroid antibodies may not be detectable at presentation or even on long-term follow-up, but their absence requires consideration of other disease entities.

Thyroid eye disease has an early inflammatory stage, typically lasting 18–36 months, where there is active lymphocytic infiltration into retrobulbar tissues. The active inflammatory stage then tends to evolve to a chronic, fibrotic, “burned out” stage in which treatment of the exophthalmos is medically resistant to glucocorticoid treatment. Aggravation of thyroid eye disease has occurred after ^{131}I treatment (see Radioactive iodine, above) or during therapy with thiazolidinediones (eg, pioglitazone); the presence of thyroid eye disease is a relative contraindication to ^{131}I treatment. Cigarette smoking increases the severity of thyroid eye disease, and ethanol injection of thyroid nodules have been reported to be followed by severe disease.

► Clinical Findings

The primary clinical features of thyroid eye disease of any etiology include upper eyelid retraction, lid lag with downward gaze, and a staring appearance. There can be proptosis, conjunctival chemosis, episcleral inflammation, and weakness of upward gaze. Corneal drying may occur with inadequate lid closure. Eye changes may sometimes be asymmetric or unilateral. Resulting symptoms are cosmetic abnormalities and surface irritation. Patients with severe exophthalmos can experience diplopia from extraocular muscle entrapment and optic nerve compression, causing progressive loss of color vision, visual acuity, and visual fields (inferior especially).

Symptoms of active retrobulbar inflammation include (1) retrobulbar aching, (2) orbital inflammation and edema worse after recumbent sleep, (3) edematous or erythematous eyelids, (4) conjunctival redness or chemosis (edema), (5) recent progression in exophthalmos, (6) recent diplopia or strabismus, and (7) recent loss of visual acuity.

Exophthalmometry should be performed on all patients with Graves disease to document their degree of exophthalmos and detect progression of orbitopathy. The protrusion of the eye beyond the orbital rim is measured with a prism instrument (Hertel exophthalmometer). Maximum normal eye protrusion varies between kindreds and races, being about 24 mm for Blacks, 20 mm for Whites, and 18 mm for Asians.

The primary imaging features are enlargement of the extraocular muscles, usually affecting both orbits.

► Differential Diagnosis

The clinical and imaging abnormalities of thyroid eye disease may be mimicked by congenital proptosis, asymmetry in orbital protrusion, or dural carotid-cavernous sinus fistula. Ocular myasthenia and thyroid eye disease are associated and may coexist, with the presence of ptosis rather than lid retraction being more characteristic of the former.

► Treatment

General eye protective measures include wearing glasses to protect the protruding eye and taping the lids shut during sleep if corneal drying is a problem. Methylcellulose drops and gels (“artificial tears”) may also help. Patients with mild thyroid eye disease may be treated with selenium 100 mcg orally twice daily, which may slow its progression.

The Mourits clinical activity score helps grade the severity of thyroid eye disease. Therapy in addition to selenium is warranted for active thyroid eye disease with a clinical activity point score greater than or equal to 3. One point is given for each of the following manifestations: (1) pain or pressure in the periorbital area, (2) pain with eye movement, (3) swelling of the eyelids, (4) erythema of the eyelids, (5) conjunctival injection, (6) chemosis, (7) caruncle inflammation, (8) increase in proptosis of 2 mm or more within 3 months, (9) decrease in eye movement within 3 months, (10) decrease in visual acuity within 3 months.

Therapy with intravenous pulse methylprednisolone, 500 mg weekly for 6 weeks, then 250 mg weekly for 6 weeks, begun promptly for active thyroid eye disease, is superior to oral prednisone. If oral prednisone is used, 40–60 mg daily with dosage reduction over several weeks must be given promptly. Higher initial daily prednisone doses of 80–120 mg are used when there is optic nerve compression. Prednisone alleviates acute eye symptoms in 64% of nonsmokers but in only 14% of cigarette smokers.

Corticosteroid-resistant acute thyroid eye disease may be treated with monoclonal antibodies that reduce immune-mediated inflammation. Teprotumumab or tocilizumab is administered intravenously; rituximab may be given by retro-orbital injection.

Progressive active exophthalmos may be treated with retrobulbar radiation therapy over 2 weeks. Prednisone in high doses is given concurrently. Patients who respond well to orbital radiation include those with signs of acute inflammation, recent exophthalmos (less than 6 months), or optic nerve compression. Patients with chronic proptosis and orbital muscle restriction respond less well. Retrobulbar radiation does not cause cataracts or tumors; however, it can cause radiation-induced retinopathy (usually subclinical) in about 5% of patients overall, mostly in patients with diabetes.

Diplopia should be treated conservatively (eg, with prisms) in the active stages of the disease and only by surgery when the disease has been static for at least 6 months. For severe cases, orbital decompression surgery may save vision, though diplopia often persists postoperatively. Tarsorrhaphy or canthoplasty can frequently help protect the cornea and provide improved appearance.

► When to Refer

All patients with thyroid eye disease should be referred to an ophthalmologist, urgently if there is reduced vision.

- Douglas RS et al. Teprotumumab for the treatment of active thyroid eye disease. *N Engl J Med.* 2020;382:341. [PMID: 31971679]
 Kumari R et al. Advances in the management of thyroid eye diseases: an overview. *Int Ophthalmol.* 2018;38:224. [PMID: 28822031]
 Taylor PN et al. New insights into the pathogenesis and nonsurgical management of Graves orbitopathy. *Nat Rev Endocrinol.* 2020;16:104. [PMID: 31889140]

THYROID NODULES & MULTINODULAR GOITER



ESSENTIALS OF DIAGNOSIS

- ▶ Single or multiple thyroid nodules are commonly palpated by the patient or clinician or discovered incidentally on imaging studies.
- ▶ Thyroid function tests recommended.
- ▶ FNA cytology for thyroid nodules ≥ 1 cm or for smaller nodules when prior head-neck or chest-shoulder radiation.
- ▶ Ultrasound guidance improves FNA diagnosis for palpable and nonpalpable nodules.
- ▶ Clinical follow-up required.

► General Considerations

Thyroid nodules are extremely common. Palpable nodules occur in 4–7% of all adults in the United States. They are much more common in women than men and become

more prevalent with age. About 87% of palpable thyroid nodules (1 cm or larger) are benign adenomas, colloid nodules, or cysts, but some are primary thyroid malignancies or (less frequently) metastatic malignancy. On MRI, incidental small thyroid nodules are found in about 50% of adults. Thyroid nodules 1 cm or larger warrant follow-up and further testing for function and malignancy; an occasional smaller nodule requires follow-up if it has high-risk characteristics on ultrasound or if the patient is at high-risk for thyroid cancer due to prior head-neck radiation therapy during childhood. Thyroid nodules that are incidentally discovered with increased standard uptake value (SUV) on ^{18}FDG -PET scanning have a 33% risk for being malignant and require FNA cytology.

Most patients with a thyroid nodule are euthyroid, but there is a high incidence of hypothyroidism or hyperthyroidism. Patients with multiple thyroid nodules have the same overall risk of thyroid cancer as patients with solitary nodules. The risk of a thyroid nodule being malignant is higher in men and among patients with a history of head-neck radiation, total body radiation for bone marrow transplantation, exposure to radioactive fallout as a child or teen, a family history of thyroid cancer or a thyroid cancer syndrome (eg, Cowden syndrome, multiple endocrine neoplasia type 2, familial polyposis, Carney syndrome), or a personal history of another malignancy. The risk of malignancy is also higher for large solitary nodules and if there is hoarseness or vocal fold paralysis, adherence to the trachea or strap muscles, cervical lymphadenopathy. The presence of autoimmune thyroiditis does not reduce the risk of malignancy; a nodule of 1 cm or larger in a gland with thyroiditis carries an 8% chance of malignancy.

► Clinical Findings

Table 26–6 illustrates how to evaluate thyroid nodules based on the index of suspicion for malignancy.

Table 26–6. Clinical evaluation of thyroid nodules.¹

Clinical Evidence	Low Index of Suspicion	High Index of Suspicion
History	Family history of goiter; residence in area of endemic goiter	Previous therapeutic radiation of head, neck, or chest; hoarseness
Physical characteristics	Older women; soft nodule; multinodular goiter	Young adults, men; solitary, firm nodule; vocal fold paralysis; enlarged lymph nodes; distant metastatic lesions
Serum factors	High titer of thyroid peroxidase antibody; hypothyroidism; hyperthyroidism	Elevated serum calcitonin
Fine-needle aspiration biopsy	Colloid nodule or adenoma	Papillary carcinoma, follicular lesion, medullary or anaplastic carcinoma
Scanning techniques		
Uptake of ^{123}I	Hot nodule	Cold nodule
Ultrasonogram	Cystic lesion	Solid lesion
Radiograph	Shell-like calcification	Punctate calcification
Response to levothyroxine therapy	Regression after 0.05–0.1 mg/day for 6 months or more	Increase in size

¹Clinically suspicious nodules should be evaluated with fine-needle aspiration biopsy.

A. Symptoms and Signs

Most small thyroid nodules cause no symptoms. They may sometimes be detected only by having the patient swallow during inspection and palpation of the thyroid.

A thyroid nodule or multinodular goiter can grow to become visible and of concern to the patient. Particularly large nodular goiters can become a cosmetic embarrassment. Nodules can grow large enough to cause discomfort, hoarseness, or dysphagia. Nodules that cause ipsilateral recurrent laryngeal nerve palsy are more likely to be malignant. Retrosternal large multinodular goiters can cause dyspnea due to tracheal compression. Large substernal goiters may cause superior vena cava syndrome, manifested by facial erythema and jugular vein distention that progress to cyanosis and facial edema when both arms are kept raised over the head.

Goiters and thyroid nodules may be associated with hypothyroidism (autoimmune thyroiditis, endemic goiter) or hyperthyroidism (Graves disease, toxic nodular goiter, subacute thyroiditis, and thyroid cancer with metastases).

B. Laboratory Findings

A serum TSH and FT₄ determine if the thyroid is hyperfunctioning. Patients with a subnormal serum TSH must have a radionuclide (¹²³I or ^{99m}Tc pertechnetate) thyroid scan to examine whether the nodule is hyperfunctioning; hyperfunctioning nodules are usually benign but not reliably so. Very high levels of TPO Ab and Tg Ab are found in autoimmune thyroiditis. However, thyroiditis frequently coexists with malignancy, so suspicious nodules should always be biopsied. Serum calcitonin is obtained if a medullary thyroid carcinoma is suspected in a patient with a family history of medullary thyroid carcinoma or MEN types 2 or 3.

C. Imaging

Neck ultrasonography should be performed (see Fine-Needle Aspiration of Thyroid Nodules, below). Malignant nodules are more likely to grow more than 2 mm/year. Ultrasonography is preferred over CT and MRI. CT scanning is helpful for larger thyroid nodules and multinodular goiter; it can determine the degree of tracheal compression and the degree of extension into the mediastinum. Thyroid nodules that are moderately to markedly hypoechoic are more likely to be malignant than nodules that are mildly hypoechoic. Nodules with heterogeneous hypoechoogenicity are also more likely to be malignant than nodules that are hyperechoic.

RAI (¹²³I or ¹³¹I) scans are not helpful for assessing whether a thyroid nodule is benign or malignant. Hyperfunctioning (hot) nodules are ordinarily benign (but may rarely be malignant). RAI uptake and scanning is helpful mainly for assessing the etiology of hyperthyroidism (eg, hyperfunctioning nodule). In hyperthyroid patients, high RAI uptake into nodules makes therapy with ¹³¹I potentially possible.

D. Incidentally Discovered Thyroid Nodules

Thyroid nodules are frequently discovered as an incidental finding, with an incidence that depends on the imaging

modality: ultrasound, about 30% (20% are larger than 1 cm); MRI, 50%; CT, 13%; and ¹⁸FDG-PET, 2%. When MRI, CT, and ¹⁸FDG-PET detect a thyroid nodule, an ultrasound is performed to better determine the nodule's risk for malignancy and the need for FNA cytology, and to establish a baseline for ultrasound follow-up. The malignancy risk is about 13–17% for nodules discovered incidentally on CT, MRI, or ultrasound and 25–50% for nodules discovered incidentally by ¹⁸FDG-PET. However, most such malignancies are very low grade. For incidentally discovered thyroid nodules of borderline concern, follow-up thyroid ultrasound in 3–6 months may be helpful; growing lesions should be assessed with FNA cytology or resected.

E. Fine-Needle Aspiration of Thyroid Nodules

FNA is the best method to assess a thyroid nodule for malignancy. FNA can be done while patients continue taking anticoagulants or aspirin. For multinodular goiters, the four largest nodules (1 cm or larger) are usually biopsied to minimize the risk of missing a malignancy.

Thyroid nodules are classified for malignancy risk according to their appearance on ultrasound. High-risk nodules (80% malignancy risk) have microcalcifications, irregular margins, extrathyroidal extension, extrusion of soft tissue into a calcified rim, or are taller than wide; such nodules require FNA if they are 1 cm or larger. Intermediate-risk nodules (15% malignancy risk) are hypoechoic and solid; they also usually require FNA if they are 1 cm or larger. Low-risk nodules (7% malignancy risk) are partially cystic with eccentric solid areas; they require biopsy if they are 1.5 cm or larger. Very low-risk nodules (below 3% malignancy risk) are those that are spongiform or simple cysts; FNA is optional if they are 2 cm or larger. Using ultrasound guidance for FNA biopsy improves the diagnostic accuracy for both palpable and nonpalpable thyroid nodules. FNA cytology is typically reported using The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), which divides results into six categories:

1. **Nondiagnostic or unsatisfactory:** The malignancy risk is 1–4%. The usual management is a repeat FNA under ultrasound guidance.
2. **Benign:** The malignancy risk is about 2.5%. The usual management is clinical follow-up with palpation or ultrasound at 6- to 18-month intervals.
3. **Atypia of undetermined significance (AUS):** The malignancy risk is about 14%, higher with sonographic features of malignancy. The usual management is clinical correlation and a repeat FNA.
4. **Suspicious for follicular neoplasm (SFN) or follicular neoplasm (FN):** The malignancy risk is about 25%, higher when Hürthle cells are present and in patients over age 50. The usual management is thyroid lobectomy.
5. **Suspicious for malignancy (SFM):** The malignancy risk is about 70%. The usual management is thyroid lobectomy or near-total thyroidectomy.
6. **Malignant:** The malignancy risk is about 99%. The usual management is a near-total thyroidectomy.

► Treatment

All thyroid nodules, including those that are benign, need to be monitored by regular periodic palpation and ultrasound about every 6 months initially. After several years of stability, yearly examinations are sufficient. Thyroid nodules should be rebiopsied if growth occurs. Excessive iodine intake should be minimized; a toxic multinodular goiter and hyperthyroidism may develop in patients who have had exposure to large amounts of iodine, either orally (eg, amiodarone) or intravenously (eg, radiographic contrast).

The treatment of hyperthyroidism from thyroid nodules or multinodular goiter with propranolol, thioureas, surgery, or RAI is similar to the treatment of hyperthyroidism from a toxic nodular goiter (see above).

A. Levothyroxine Suppression Therapy

Patients with nodules larger than 2 cm and elevated or normal TSH levels may be considered for TSH suppression with levothyroxine (starting doses of 50 mcg orally daily). Levothyroxine suppression therapy is not recommended for small benign thyroid nodules if the serum TSH level is normal. Levothyroxine suppression therapy is more successful in iodine-deficient areas. Long-term levothyroxine suppression of TSH tends to keep nodules from enlarging but only 20% shrink more than 50%. Thyroid nodule size increased in 29% of patients treated with levothyroxine versus 56% of patients not receiving levothyroxine. Levothyroxine suppression also reduces the emergence of new nodules: 8% with levothyroxine and 29% without levothyroxine. Levothyroxine suppression therapy is not usually given to patients with ischemic heart disease, since it increases the risk for angina and atrial fibrillation. Levothyroxine suppression causes a small loss of bone density, particularly in postmenopausal women if the serum TSH is suppressed to less than 0.05 milli-international units/L. Such patients are advised to have bone density testing every 3–5 years. For patients with a low baseline TSH level, levothyroxine should not be administered, since that is an indication of autonomous thyroid secretion; levothyroxine will be ineffective and could cause thyrotoxicosis.

Levothyroxine suppression needs to be carefully monitored, since it carries a 17% risk of inducing hyperthyroidism. All patients receiving levothyroxine suppression therapy should have serum TSH levels monitored at least annually, with the levothyroxine dose adjusted to keep the serum TSH mildly suppressed (between 0.1 milli-international units/L and 0.8 milli-international units/L).

B. Surgery

Total thyroidectomy is required for thyroid nodules that are malignant on FNA biopsy. More limited thyroid surgery is indicated for benign nodules with indeterminate or suspicious cytologic test results, compression symptoms, discomfort, or cosmetic embarrassment. Surgery may also be used to remove hyperfunctioning “hot” thyroid adenomas or toxic multinodular goiter causing hyperthyroidism.

C. Radiofrequency and Alcohol Ablation

Ultrasound-guided radiofrequency ablation is a therapeutic option for cytology-proven benign thyroid nodules that are 3 cm or larger and predominantly solid. Radiofrequency ablation shrinks such nodules by about 67% after 6 months, improving pressure symptoms and dysphagia in most patients and reducing the size of cosmetically embarrassing thyroid nodules. Side effects include mild neck discomfort, swelling, bruising, and dysphagia that generally resolves within 5 days. Radiofrequency ablation of thyroid nodules close to the vagus nerve may cause temporary vasovagal hypotension. Radiofrequency ablation-induced damage to the recurrent laryngeal nerve can cause hoarseness. Radiofrequency ablation-induced rupture of a thyroid nodule presents as acute neck swelling and pain; most such patients recover spontaneously, but some may require neck aspiration or surgical incision and drainage. Ultrasound-guided alcohol ablation can be useful for predominantly cystic thyroid nodules that are unassociated with Graves disease. However, recurrence is common.

D. Radioiodine (¹³¹I) Therapy

¹³¹I is a treatment option for hyperthyroid patients with toxic thyroid adenomas, multinodular goiter, or Graves disease. See **Precautions** for RAI use, above. Therapy with ¹³¹I shrinks benign nontoxic thyroid nodules by an average of 40% by 1 year and 59% by 2 years after ¹³¹I therapy. Nodules that shrink after ¹³¹I therapy generally remain palpable and become firmer; they may develop unusual cytologic characteristics on FNA biopsy. ¹³¹I therapy may be used to shrink large multinodular goiters but may rarely induce Graves disease. Hypothyroidism may occur years after ¹³¹I therapy; it is advisable to assess thyroid function every 3 months for the first year, every 6 months thereafter, and immediately for symptoms of hypothyroidism or hyperthyroidism.

► Prognosis

Benign thyroid nodules may involute but usually persist or grow slowly. About 90% of thyroid nodules will increase their volume by 15% or more over 5 years; about 11% of nodules increase their volume by more than 50% on follow-up. Growth is more common with multinodular goiter and larger nodules and in men; nodules are less likely to grow when they are solitary or cystic and when patients are over age 60. Multinodular goiters tend to persist or grow slowly. Cytologically benign nodules that grow are unlikely to be malignant; in one series, only 1 of 78 rebiopsied nodules was found to be malignant. The risk of a given thyroid nodule being malignant decreases with age. Iodine supplementation in iodine-deficient areas does not usually shrink established goiters. Patients with very small (less than 1 cm), incidentally discovered, nonpalpable thyroid nodules that have a benign ultrasound appearance require no FNA cytology and only yearly palpation and clinical follow-up, whereas such small nodules that have a slightly suspicious ultrasound appearance may require FNA cytology or thyroid ultrasound every 1–2 years.

Durante C et al. The diagnosis and management of thyroid nodules: a review. *JAMA*. 2018;319:914. [PMID: 29509871]
 Le JY et al. Ultrasound malignancy risk stratification of thyroid nodules based on the degree of hypoechogenicity and echotexture. *Eur Radiol*. 2020;30:1653. [PMID: 31732777]
 Maxwell C et al. Clinical diagnostic evaluation of thyroid nodules. *Endocrinol Metab Clin North Am*. 2019;48:61. [PMID: 30717911]

THYROID CANCER



ESSENTIALS OF DIAGNOSIS

- ▶ Painless swelling in region of thyroid.
- ▶ Thyroid function tests are usually normal.
- ▶ Differentiated thyroid carcinomas: papillary and follicular.
- ▶ Medullary thyroid carcinoma.
- ▶ Anaplastic thyroid carcinoma.
- ▶ Possible history of childhood irradiation to head and neck region.
- ▶ Positive thyroid FNA cytology.

► General Considerations

The incidence of differentiated (papillary and follicular) thyroid carcinomas increases with age (Table 26–7). The overall female:male ratio is 3:1. The yearly incidence of thyroid cancer has been increasing in the United States, with the number of cases diagnosed annually reaching 52,000, probably as a result of the wider use of ultrasound, CT, MRI, and positron emission tomography (PET) that incidentally find mostly small thyroid malignancies. Thyroid cancer mortality has been stable, accounting for about 2000 deaths in the United States annually. In routine autopsy series, thyroid papillary microcarcinoma (10 mm or smaller) is found with the surprising frequency of 11.5%. Most thyroid cancers remain microscopic and indolent. However, larger thyroid cancers (palpable or 1 cm or larger) are more malignant and require treatment.

Pure papillary (and mixed papillary-follicular) carcinoma comprises about 80% of all thyroid cancers. It usually presents as a single thyroid nodule, but it can arise out of a multinodular goiter. Papillary thyroid carcinoma is commonly multifocal within the gland, with other foci usually arising de novo rather than representing intraglandular metastases. The tumor involves both lobes in 30% of patients.

Papillary thyroid carcinoma is the least aggressive thyroid malignancy. It tends to grow slowly and often remains confined to the thyroid and regional lymph nodes for years. In about 80% of patients, there are microscopic metastases to cervical lymph nodes. The malignancy may become more aggressive, however, especially in patients over age 45 years, and most particularly in older adults. The cancer may invade the trachea and local muscles and may spread to the lungs.

Childhood exposure to head and neck radiation therapy poses a particular threat because of an increased lifetime risk of developing thyroid cancer, including papillary carcinoma. These cancers may emerge 10–40 years after exposure, with a peak occurrence 20–25 years later.

Papillary thyroid carcinoma can occur in familial syndromes as an autosomal dominant trait, caused by loss of various tumor suppressor genes.

Microscopic “micropapillary” carcinoma (1 mm or smaller and invisible on thyroid ultrasound) is a variant of normal, being found in 24% of thyroidectomies performed for benign thyroid disease when 2-mm sections were carefully examined. The overwhelming majority of these microscopic foci never become clinically significant. The surgical pathology report of such tiny papillary carcinomas do not justify aggressive measures. All that may be required is yearly follow-up with palpation of the neck and mild TSH suppression by thyroxine.

Follicular thyroid carcinoma and its variants (eg, Hürthle cell carcinoma) account for about 14% of thyroid malignancies; follicular carcinomas are generally more aggressive than papillary carcinomas. Most follicular thyroid carcinomas avidly absorb iodine, making possible diagnostic scanning and treatment with ^{131}I after total thyroidectomy. The follicular histopathologic features that are associated with a high risk of metastasis and recurrence

Table 26–7. Some characteristics of thyroid cancer.

	Papillary	Follicular	Medullary	Anaplastic
Incidence	Most common	Common	Uncommon	Uncommon
Average age (years)	42	50	50	57
Females	70%	72%	56%	56%
Invasion				
Juxtanodal	+++++	+	+++++	+++
Blood vessels	+	+++	+++	++++
Distant sites	+	+++	++	+++
^{123}I uptake	+	++++	0	0
10-year disease-specific survival	97%	92%	78%	7.3%

are poorly differentiated and Hürthle cell (oncocytic) variants. The latter variants do not take up RAI.

Medullary thyroid carcinoma represents 2–3% of thyroid cancers. About one-third of cases are sporadic, one-third are familial, and one-third are associated with MEN type 2A or 2B. Medullary thyroid carcinoma is often caused by an activating mutation of the *ret* protooncogene on chromosome 10. Mutation analysis of the *ret* protooncogene exons 10, 11, 13, 14, and 16 detects most mutations causing MEN 2A and MEN 2B and the mutations causing familial medullary thyroid carcinoma. Therefore, discovery of a medullary thyroid carcinoma makes genetic analysis mandatory. If a gene defect is discovered, related family members must have genetic screening for that gene defect. When a family member with MEN 2 or 3 or familial medullary thyroid carcinoma does not have an identifiable *ret* protooncogene mutation, gene carriers may still be identified using family linkage analysis. Even when no gene defect is detectable, family members should have thyroid surveillance every 6 months. Medullary thyroid carcinoma arises from thyroid parafollicular cells that can secrete calcitonin, prostaglandins, serotonin, ACTH, corticotropin-releasing hormone (CRH), and other peptides. These peptides can cause symptoms and can be used as tumor markers.

Anaplastic thyroid carcinoma represents about 2% of thyroid cancers. It usually presents in an older patient as a rapidly enlarging mass in a multinodular goiter. It is the most aggressive thyroid carcinoma and metastasizes early to surrounding nodes and distant sites. This tumor does not concentrate iodine which precludes the therapeutic use of RAI.

Other thyroid malignancies together represent about 3% of thyroid cancers. Primary thyroid lymphomas are most commonly diffuse large B-cell lymphomas (50%), mucosa-associated lymphoid tissue lymphoma (23%), or mixed type; other types include follicular, small lymphocytic, and Burkitt lymphoma and Hodgkin disease. Thyroidectomy is rarely required. Other cancers may sometimes metastasize to the thyroid, particularly bronchogenic, breast, and renal carcinomas and malignant melanoma.

► Clinical Findings

A. Symptoms and Signs

Thyroid carcinoma usually presents as a palpable, firm, nontender nodule in the thyroid. Most thyroid carcinomas are asymptomatic, but large thyroid cancers can cause neck discomfort, dysphagia, or hoarseness (due to pressure on the recurrent laryngeal nerve). **Papillary thyroid cancer** presents with palpable lymph node involvement in 10%; it may invade the trachea and local muscles. Occult metastases to the lung occur in 10–15%. **Follicular thyroid carcinoma** commonly metastasizes to neck nodes, bones, and lung, but nearly every organ can be involved.

Medullary thyroid carcinoma typically metastasizes to local nodes and adjacent muscle and trachea as well as mediastinal lymph nodes. Eventually, metastases may appear in the bones, lungs, adrenals, or liver. Medullary

thyroid carcinoma frequently causes flushing and persistent diarrhea (30%), which may be the initial clinical feature. Patients with metastases often experience fatigue as well as other symptoms. Cushing syndrome develops in about 5% of patients from secretion of ACTH or CRH.

Anaplastic thyroid carcinoma is more apt to be advanced at the time of diagnosis, presenting with signs of pressure or invasion of surrounding tissue, resulting in dysphagia, hoarseness, or recurrent laryngeal nerve palsy. Patients may also have dyspnea with metastases to the lungs. **Lymphoma** usually presents as a rapidly enlarging, painful mass arising out of a multinodular or diffuse goiter due to autoimmune thyroiditis, with which it may be confused microscopically. About 20% of cases have concomitant hypothyroidism.

B. Laboratory Findings

FNA biopsy is discussed in Thyroid Nodules, above. Thyroid function tests are generally normal unless there is concomitant thyroiditis. However, with a heavy tumor burden, functioning follicular or papillary thyroid carcinomas can sometimes secrete enough thyroid hormone to produce thyrotoxicosis and suppress the serum TSH.

Serum thyroglobulin is high in most metastatic papillary and follicular tumors, making this a useful marker for recurrent or metastatic disease. Caution must be exercised for the following reasons: (1) Circulating Tg Ab can cause erroneous thyroglobulin determinations. However, declining levels of Tg Ab are a good prognostic sign after treatment. (2) Thyroglobulin levels may be misleadingly elevated in thyroiditis, which often coexists with carcinoma. (3) Certain thyroglobulin assays falsely report the continued presence of thyroglobulin after total thyroidectomy and tumor resection, causing undue concern about possible metastases. Therefore, unexpected detectable thyroglobulin levels post-thyroidectomy should prompt a repeat assay in another reference laboratory.

Serum calcitonin is usually elevated in medullary thyroid carcinoma, making this a marker for metastatic disease. However, serum calcitonin may be elevated in thyroiditis; pregnancy; kidney disease; hypergastrinemia; hypercalcemia; and other malignancies, particularly neuroendocrine tumors (including pheochromocytomas, carcinoid tumors) and carcinomas of the lung, pancreas, breast, and colon. Serum calcitonin and carcinoembryonic antigen (CEA) determinations should be obtained before surgery, then regularly in postoperative follow-up: every 4 months for 5 years, then every 6 months for life. In patients with extensive metastases, serum calcitonin should be measured in the laboratory with serial dilutions. Calcitonin levels remain elevated in patients with persistent tumor but also in some patients with apparent cure or indolent disease. Therefore, serum calcitonin levels greater than 250 ng/L (73 pmol/L) or rising levels of calcitonin are the best indication for recurrence or metastatic disease. Serum CEA levels are also usually elevated with medullary thyroid carcinoma, making this a useful second marker; however, it is not specific for this cancer.

C. Imaging

1. Ultrasound of the neck—Ultrasound of the neck should be performed on all patients with thyroid cancer for the initial diagnosis and for follow-up. Ultrasound is useful in determining the size and location of the malignancy as well as the location of any neck metastases.

2. Radioactive iodine scanning—RAI (^{131}I or ^{123}I) thyroid and whole-body scanning is used after thyroidectomy for differentiated thyroid cancer utilizing the protocol described later. (See Radioactive Iodine (^{131}I) Therapy for Differentiated Thyroid Cancer, below.) Medullary thyroid cancer does not avidly uptake RAI.

3. CT and MRI scanning—CT scanning may demonstrate metastases and is particularly useful for localizing and monitoring lung metastases but is less sensitive than ultrasound for detecting metastases within the neck. Medullary carcinoma in the thyroid, nodes, and liver may calcify, but lung metastases rarely do so. MRI is particularly useful for imaging bone metastases.

4. PET scanning—PET scanning is especially helpful for detecting thyroid cancer metastases that do not have sufficient iodine uptake to be visible on RAI scans. Thyroid cancer metastases may be detected with ^{18}FDG -PET whole-body scanning. The sensitivity of ^{18}FDG -PET scanning for differentiated thyroid cancer is enhanced if the patient is hypothyroid or receiving thyrotropin, which increases the metabolic activity of differentiated thyroid cancer. Patients with medullary thyroid cancer are monitored with MRI and ^{18}FDG PET/CT scanning. However, ^{68}Ga -DOTATATE-PET imaging is superior for detecting medullary thyroid cancer metastases in certain patients, particularly those with very high serum calcitonin levels (above 500 pg/mL). Although ^{68}Ga -DOTATATE-PET is more specific for neuroendocrine tumors, other malignancies express somatostatin receptors and can have misleading uptake on this scan, including non-Hodgkin lymphoma, meningioma, breast cancer, thyroid adenoma, and papillary thyroid carcinoma.

Differential Diagnosis

Head-neck RAI uptake is seen in normal thyroid, salivary glands, nasal mucosa, thyroglossal duct remnants, and sinuses.

Negative RAI scans are common in early metastatic differentiated thyroid carcinoma. Negative RAI scans also occur frequently with more advanced metastatic thyroid carcinoma, making it more difficult to detect and to distinguish from nonthyroidal neoplasms. An elevated serum thyroglobulin in patients with a clear RAI scan should arouse suspicion for metastases that are not avid for RAI. Medullary thyroid carcinoma does not concentrate iodine.

Complications

Hyperthyroidism can develop in patients with a heavy tumor burden. One-third of medullary thyroid carcinomas secrete serotonin and prostaglandins, producing flushing and diarrhea. The management of patients with medullary

carcinomas may be complicated by the coexistence of pheochromocytomas or hyperparathyroidism.

Treatment of Differentiated Thyroid Carcinoma

A. Surgical Treatment

Surgical removal is the treatment of choice for thyroid carcinomas. Neck ultrasound is obtained preoperatively, since suspicious cervical lymphadenopathy is detected in about 25%.

For differentiated papillary and follicular carcinoma larger than 1 cm, total thyroidectomy is performed with limited removal of cervical lymph nodes. Surgery consists of a thyroid lobectomy for an indeterminate “follicular lesion” that is 4 cm or smaller. If malignancy is diagnosed on pathology intraoperatively, a completion thyroidectomy is performed. For indeterminate follicular lesions larger than 4 cm that are at higher risk for being malignant, a bilateral thyroidectomy is performed as the initial surgery. Higher-risk lesions include those with an FNA biopsy that shows marked atypia or that are suspicious for papillary carcinoma and those that occur in patients with a history of radiation exposure or a family history of thyroid carcinoma.

For papillary thyroid carcinoma, surgery involves lobectomy alone for cancers smaller than 1 cm in patients under age 45 years who have no history of head and neck irradiation and no evidence of lymph node metastasis on ultrasonography. Other patients should have a total or near total thyroidectomy. The advantage of near-total thyroidectomy for differentiated thyroid carcinoma is that multicentric foci of carcinoma are more apt to be resected. Also, there is less normal thyroid tissue to compete with cancer for ^{131}I administered later for scans or treatment. A central neck lymph node dissection is performed at the time of thyroidectomy for patients with nodal metastases that are clinically evident. A lateral neck dissection is performed for patients with biopsy-proven lateral cervical lymphadenopathy. Metastases to the brain are best treated surgically, since treatment with radiation or RAI is ineffective. Levothyroxine, 0.05–0.1 mg orally daily, is begun immediately postoperatively. About 2–4 months after surgery, patients require reevaluation and often ^{131}I therapy.

Permanent injury to one recurrent laryngeal nerve occurs in 1% and 7% of patients, depending on surgical expertise. Temporary recurrent laryngeal nerve palsies occur in another 5% but often resolve within 6 months. After total thyroidectomy, temporary hypoparathyroidism occurs in 20% and becomes permanent in about 2%. The incidence of hypoparathyroidism may be reduced if accidentally resected parathyroids are immediately autotransplanted into the neck muscles. Thyroidectomy requires at least an overnight hospital admission, since late bleeding, airway problems, and tetany can occur. *Ambulatory thyroidectomy is potentially dangerous and should not be done.* Following surgery, staging (Table 26–8) should be done to help determine prognosis and to plan therapy and follow-up.

In pregnant women with thyroid cancer, surgery is usually delayed until after delivery, except for fast-growing tumors that may be resected after 24 weeks' gestation; there

Table 26–8. Staging and prognosis for patients with papillary thyroid carcinoma using MACIS scoring.

Total Score ¹ - Stage	Percentage of Patients with Papillary Thyroid Carcinoma	20-Year Survival
< 6.0 = Stage I	74.2%	96–99%
6.0–6.99 = Stage II	8.5%	68–89%
7.0–7.99 = Stage III	9.2%	55–56%
≥ 8.0 = Stage IV	8.1%	17–24%

¹Total score = 3.1 (if aged \leq 39 years) or $0.08 \times$ age (if aged \geq 40 years) + $0.3 \times$ tumor size (cm), +1 (if incompletely resected), +1 (if locally invasive), +3 (if distant metastases).

MACIS, metastases, age, complete resection, invasion, size.

has been no difference in survival or tumor recurrence rates in women who underwent surgery during or after their pregnancy. Differentiated thyroid carcinoma does not behave more aggressively during pregnancy. However, compared to nonpregnant women, there is a higher risk of complications in pregnant women undergoing thyroid surgery.

B. Active Surveillance for Papillary Thyroid Microcarcinoma

Most papillary thyroid microcarcinomas that are less than 1 cm are indolent with an excellent prognosis. For such microcarcinomas, an ongoing active surveillance protocol used in some medical centers consists of performing a clinical examination and neck ultrasound every 6 months. Such conservative management may be particularly warranted for patients who have a limited life expectancy, a high surgical risk, or very low-risk tumors.

C. Levothyroxine Suppression of Thyroid-Stimulating Hormone

Levothyroxine is prescribed for differentiated thyroid cancer in doses to achieve a target serum TSH: (1) For initial TSH suppression in patients with stage II–IV disease, the target serum TSH is below 0.1 milli-international units/L while avoiding clinical hyperthyroidism; (2) For initial TSH suppression in patients with stage I disease and for 5–10 years after remission in previously stage II–IV patients, the target TSH is between 0.1 and 0.5 milli-international units/L; (3) For patients who are free of disease and at low risk for recurrence, the target TSH is 0.5–2 milli-international units/L.

D. Radioactive Iodine (^{131}I) Therapy for Differentiated Thyroid Cancer

There are two reasons to treat patients with ^{131}I after thyroidectomy: (1) thyroid remnant ablation for patients at high risk for recurrence and (2) treatment of metastatic thyroid cancer. ^{131}I is usually administered 2–4 months after surgery. However, the indications and optimal activity (dose) for ^{131}I therapy for differentiated thyroid cancer

remain controversial, since the prognosis for most patients is overwhelmingly good.

Before receiving ^{131}I therapy, patients should follow a low-iodine diet for at least 2 weeks. Patients must not be given amiodarone or intravenous radiologic contrast dyes containing iodine. Despite restriction of dietary iodine, differentiated thyroid cancer frequently lacks sufficient RAI avidity to allow RAI therapy.

1. RAI thyroid remnant ablation—A low activity¹ of 30 mCi (1.1 GBq) ^{131}I is sometimes given for “remnant ablation” of residual normal thyroid tissue after surgery for differentiated thyroid cancer in patients without known metastases. However, ^{131}I remnant ablation is not required for patients with low-risk stage I papillary thyroid carcinomas or carcinomas that are smaller than 1 cm (whether unifocal or multifocal), except for patients with unfavorable histopathology (tall-cell, columnar cell, insular cell, Hürthle cell, or diffuse sclerosing subtypes).

2. RAI treatment of metastases—Therapy with ^{131}I improves survival and reduces recurrence rates of differentiated thyroid cancer for patients with stage III–IV cancer and those with stage II cancer having gross extrathyroidal extension. RAI therapy is also given to patients with stage II cancer who have distant metastases, a primary tumor larger than 4 cm, or primary tumors 1–4 cm with lymph node metastases or other high-risk features. Brain metastases do not usually respond to ^{131}I and are best resected or treated with gamma knife radiosurgery. A post-therapy whole-body scan is performed 2–10 days after ^{131}I therapy. About 70% of small lung metastases resolve following ^{131}I therapy; however, larger pulmonary metastases have only a 10% remission rate.

Staging with RAI scanning or $^{18}\text{FDG-PET/CT}$ scanning assists with determining the activity of ^{131}I to be administered. Repeated treatments may be required for persistent ^{131}I -avid metastatic disease. Patients with differentiated thyroid carcinoma who have little or no uptake of RAI into metastases (about 35% of cases) should not be treated with ^{131}I . Patients with asymptomatic, stable, RAI-resistant metastases should receive levothyroxine to suppress serum TSH and should be carefully monitored for tumor progression.

Some patients have elevated serum thyroglobulin levels but a negative whole-body RAI scan and a negative neck ultrasound. In such patients, an $^{18}\text{F-FDG PET/CT}$ scan is obtained. If all scans are negative, the patient has a good prognosis and empiric therapy with ^{131}I is not useful.

3. Recombinant human TSH (rhTSH)-stimulated ^{131}I therapy—Recombinant human thyroid-stimulating hormone (rhTSH, Thyrogen) can be given to increase the sensitivity of serum thyroglobulin for residual cancer and to increase the uptake of ^{131}I into residual thyroid tissue

¹The amount of RAI radioactivity given in a procedure is referred to as radioactivity or “activity” and is expressed as Curies (Ci) or Becquerels (Bq), whereas the term “dose” is reserved to describe the amount of radiation absorbed by a given organ or tumor and is expressed as Gray (Gy) or radiation-absorbed dose (RAD).

(thyroid remnant “ablation”) or cancer. Thyrogen is administered according to the following protocol: Levothyroxine replacement is held for 2 days before rhTSH and for 3 days afterward. For 2 consecutive days, rhTSH (0.9 mg/day, reconstituted with 0.2 mL sterile saline) should be administered intragluteally (not intravenously). On the third day, blood is drawn; serum TSH is assayed to confirm that it is greater than 30 milli-units/L; serum hCG is measured in reproductive-age women to exclude pregnancy; and serum thyroglobulin is measured as a tumor marker. RAI is then administered.

Thyrogen should not be administered to patients with an intact thyroid gland because it can cause severe thyroid swelling and hyperthyroidism. Hyperthyroidism can also occur in patients with significant metastases or residual normal thyroid. Other side effects include nausea (11%) and headache (7%). Thyrotropin has caused neurologic deterioration in 7% of patients with CNS metastases.

4. Thyroid-withdrawal stimulated ^{131}I therapy—Thyroid withdrawal is sometimes used because of its lower cost, despite the discomforts of becoming hypothyroid. Levothyroxine is withdrawn for 14 days and the patient is allowed to become hypothyroid; high levels of endogenous TSH stimulate the uptake of RAI and production of thyroglobulin by thyroid cancer or residual thyroid. Just prior to ^{131}I therapy, the following blood tests are obtained: serum TSH to confirm it is greater than 30 milli-units/L, serum hCG in reproductive-age women to screen for pregnancy, and serum thyroglobulin as a tumor marker. Three days after ^{131}I therapy, levothyroxine therapy may be resumed at full replacement dose.

5. Side effects from ^{131}I therapy—National Cancer Institute surveillance data of patients with differentiated thyroid cancer, treated with only surgery, have a 5% increased risk of developing a second non-thyroid malignancy. Patients with thyroid cancer who receive ^{131}I therapy have a further increased risk of developing a second non-thyroid malignancy (especially leukemia and lymphoma). The risk of second cancers peaks about 5 years following ^{131}I therapy.

^{131}I therapy can cause gastritis, temporary oligospermia, sialadenitis, and xerostomia. Radioiodine therapy can cause neurologic decompensation in patients with thyroid brain metastases; such patients are treated with prednisone 30–40 mg orally daily for several days before and after ^{131}I therapy. Cumulative doses of ^{131}I over 500 mCi (18.5 GBq) can cause infertility, pancytopenia (4%), and leukemia (0.3%). Pulmonary fibrosis can occur in patients with diffuse lung metastases after receiving cumulative ^{131}I activities over 600 mCi (22 GBq). The kidneys excrete RAI, so patients with advanced kidney disease require only 20% of the usual ^{131}I activity.

E. Other Therapies for Differentiated Thyroid Cancer

Patients with osteolytic metastases to bone from differentiated thyroid cancer may be treated with one of two anti-bone resorptive drugs: (1) zoledronic acid, 4 mg intravenously; or (2) denosumab, 120 mg subcutaneously. The

frequency and duration of therapy are individualized according to each patient’s symptoms and response. These drugs must be used judiciously; there is an increased risk of atypical femur fractures and osteonecrosis of the jaw with prolonged therapy with either drug.

Patients with aggressive differentiated thyroid cancers may have metastases that are refractory to ^{131}I therapy. Recurrence in the neck may be treated with surgical debulking and external beam radiation therapy. Patients with RAI-refractory differentiated thyroid cancer metastases that are advanced and rapidly progressive may be treated with tyrosine kinase inhibitors. Vandetanib and sunitinib induce partial responses in about 40%, while lenvatinib induces partial responses in about 65%. However, median progression-free survival has been only about 18 months and all tyrosine kinase inhibitors can cause serious adverse reactions, so the patient and clinician must decide whether this chemotherapy is worthwhile.

► Treatment of Other Thyroid Malignancies

Medullary thyroid carcinoma is best treated with surgery for the primary tumor and metastases. Patients with a *ret* protooncogene mutation should have a prophylactic total thyroidectomy, ideally by age 6 years (MEN 2A) or at age 6 months (MEN 2B). Medullary thyroid carcinoma does not respond to ^{131}I therapy. Patients should be monitored closely, with serum calcitonin levels checked about every 3 months. Since medullary thyroid carcinoma can be indolent, patients should be considered for chemotherapy only if they have rapidly progressive metastases, as evidenced by a doubling time of serum calcitonin or CEA doubling time less than 2 years. ^{177}Lu -DOTATATE peptide receptor radionuclide therapy (PRRT, Lutathera) is an option for patients with progressive medullary thyroid carcinoma metastases that are very avid for ^{68}Ga -DOTATATE on diagnostic imaging (Krenning uptake grade 3–4) and tumoral immunohistochemical staining that demonstrates SSTR2a receptor expression. PRRT may induce stable disease but typically does not induce remissions or improvement in symptoms. Chemotherapy is relatively ineffective for medullary thyroid carcinoma. Vandetanib and cabozantinib are approved for use against rapidly progressive metastatic medullary thyroid carcinoma; both require close observation to avoid toxicity. Patients with medullary thyroid carcinoma and diabetes should not receive diabetic therapy with glucagon-like peptide-1 (GLP-1) agonists because they may stimulate the growth of medullary thyroid carcinoma.

Anaplastic thyroid carcinoma is treated with local resection and radiation. It does not respond to ^{131}I therapy. Lovastatin has been shown to cause differentiation and apoptosis of anaplastic thyroid carcinoma cells in vitro, but clinical studies are lacking. Anaplastic thyroid cancers with mTOR mutations may be inhibited by everolimus. In patients with *BRAF^{V600E}* mutant anaplastic thyroid cancer, combined BRAF and MEK inhibition with dabrafenib and trametinib has induced durable responses.

Thyroid mucosa-associated lymphoid tissue lymphomas have a low risk of recurrence after simple thyroidectomy. Patients with other thyroid lymphomas are best

treated with external radiation therapy; chemotherapy is added for extensive lymphoma (Table 39–2).

External beam radiation therapy may be delivered to bone metastases, especially those that are without radioiodine uptake or are RAI-refractory. Local neck radiation therapy may also be given to patients with anaplastic thyroid carcinoma. Brain metastases can be treated with gamma knife radiosurgery.

► Follow-Up

Most differentiated thyroid carcinoma recurs within 5–10 years after thyroidectomy. While lifetime monitoring is recommended, the follow-up protocol can be tailored to the staging and aggressiveness of the malignancy. All patients require at least a yearly thyroid ultrasound and serum thyroglobulin level (while taking levothyroxine). Patients at higher risk usually require at least two annual consecutively negative stimulated serum thyroglobulin determinations less than 1 ng/mL and normal RAI scans (if done) and neck ultrasound scans before they are considered to be in remission. The first surveillance occurs with stimulated postoperative serum thyroglobulin, ^{131}I therapy, and post-therapy scanning about 2–4 months after surgery. At 9–12 months postoperatively, patients may receive another stimulated serum thyroglobulin and RAI scan. Patients need not have repeated ^{131}I therapies if persistent RAI uptake is confined to the thyroid bed and if neck ultrasounds appear normal and stimulated serum thyroglobulin levels remain less than 2 ng/mL. Patients with differentiated thyroid carcinoma must be monitored long term for recurrent or metastatic disease. Further RAI or other scans may be required for patients with more aggressive differentiated thyroid cancer, prior metastases, rising serum thyroglobulin levels, or other evidence of metastases.

1. Levothyroxine suppression for differentiated thyroid cancer—Patients who have had a thyroidectomy for differentiated thyroid cancer must take levothyroxine replacement for life. Oral levothyroxine should be given in doses that suppress serum TSH without causing clinical thyrotoxicosis. Serum TSH should be suppressed below 0.1–0.5 milli-international units/L for low-risk patients with stage I disease, below 0.1 milli-international units/L for patients with stage II disease, and below 0.05 milli-international units/L for patients with stage III–IV disease. (See Table 26–8.)

Patients who are considered cured should nevertheless be treated with sufficient levothyroxine to keep the serum TSH less than 2 milli-international units/L. Follow-up must include physical examinations and laboratory testing to ensure that patients remain clinically euthyroid with serum TSH levels in the target range. To achieve suppression of serum TSH, the required dose of levothyroxine may be such that serum FT_4 levels may be slightly elevated; in that case, measurement of serum T_3 or free T_3 can be useful to ensure the patient is not frankly hyperthyroid. Thyrotoxicosis can be caused by over-replacement with levothyroxine or by the growth of functioning metastases. Although patients receiving levothyroxine suppression therapy (TSH less than 0.05 milli-international units/L) are at risk for a lower bone density than age-matched controls,

the adverse effects upon bone density and fracture risk are relatively minor for patients who remain clinically euthyroid. Nevertheless, patients receiving levothyroxine suppression therapy should have periodic bone densitometry.

2. Serum thyroglobulin—Thyroglobulin is produced by normal thyroid tissue and by most differentiated thyroid carcinomas. It is only after a total or near-total thyroidectomy and ^{131}I remnant ablation that thyroglobulin becomes a useful tumor marker for patients with differentiated papillary or follicular thyroid cancer, particularly for patients who do not have serum Tg Ab.

Detectable thyroglobulin levels do not necessarily indicate the presence of residual or metastatic thyroid cancer. Conversely, baseline serum thyroglobulin levels are insensitive markers for disease recurrence. However, baseline or stimulated serum thyroglobulin levels 2 ng/mL or higher indicate the need for a repeat neck ultrasound and further scanning with RAI or $^{18}\text{FDG-PET}$. Serum thyroglobulin and RAI scanning are stimulated by either rhTSH or thyroid hormone withdrawal according to the protocols described above for ^{131}I treatment. If serum thyroglobulin levels remain 2 ng/mL or higher in the presence of normal scanning, it is prudent to repeat the serum thyroglobulin in a national reference laboratory. In one series of patients with differentiated thyroid cancer following thyroidectomy, there was a 21% incidence of metastases in patients with serum thyroglobulin less than 1 ng/mL (while receiving levothyroxine for TSH suppression). Therefore, *baseline* serum thyroglobulin levels are inadequately sensitive and *stimulated* serum thyroglobulin measurements should be used and *always* with neck ultrasound. The usefulness of routinely doing a RAI scan in low-risk patients is controversial but continues to be done in many centers during stimulation following either rhTSH or thyroid hormone withdrawal.

3. Neck ultrasound—Neck ultrasound should be used in all patients with thyroid carcinoma to supplement neck palpation; it should be performed preoperatively, 3 months postoperatively, and regularly thereafter. Ultrasound is more sensitive for lymph node metastases than either CT or MRI scanning. Small inflammatory nodes may be detected postoperatively and do not necessarily indicate metastatic disease, but follow-up is necessary. Ultrasound-guided FNA biopsy should be performed on suspicious lesions.

4. Radioactive iodine (RAI): ^{131}I or ^{123}I neck and whole-body scanning—Despite its limitations, RAI scanning has traditionally been used to detect metastatic differentiated thyroid cancer and to determine whether the cancer is amenable to treatment with ^{131}I . RAI scanning is particularly useful for high-risk patients and those with persistent Tg Ab that make serum thyroglobulin determinations unreliable.

The ^{131}I radioisotope may be used for scanning provided it is given less than 2 weeks before scheduled ^{131}I treatment to avoid “stunning” metastases such that they take up less of the RAI therapy activity. Alternatively, the ^{123}I radioisotope may also be used and does not stun tumors; it allows single-photon emission computed tomography (SPECT) to better localize metastases. Initial RAI scanning is typically performed about 2–4 months following surgery for differentiated thyroid carcinoma.

About 65% of metastases are detectable by RAI scanning but only after optimal preparation. Patients should ideally have a total or near-total thyroidectomy, since any residual normal thyroid competes for RAI with the metastases, which are less avid for iodine. It is reasonable to perform a rhTSH-stimulated scan and thyroglobulin level 2–3 months after the initial neck surgery. If the scan is negative and the serum thyroglobulin is less than 2 ng/mL, low-risk patients may not require further scanning but should continue to be monitored with neck ultrasound and serum thyroglobulin levels every 6–12 months. For higher-risk patients, the rhTSH-stimulated thyroglobulin and RAI scan may be repeated about 1 year after surgery and then again if warranted.

The combination of rhTSH-stimulated scanning and thyroglobulin levels detects a thyroid remnant or cancer with a sensitivity of 84%. However, the presence of Tg Ab renders the serum thyroglobulin determination uninterpretable. In about 21% of low-risk patients, rhTSH stimulates serum thyroglobulin to above 2 ng/mL; such patients have a 23% risk of local neck metastases and a 13% risk of distant metastases. The rhTSH-stimulated RAI neck and whole-body scan detects only about half of these metastases because they are small or not avid for iodine. Some patients have persistent RAI uptake in the neck on diagnostic scanning but have no visible tumor on neck ultrasound; such patients do not require additional RAI therapy, especially if the serum thyroglobulin level is very low.

5. Positron emission tomography scanning—¹⁸FDG-PET scanning is particularly useful for detecting differentiated thyroid cancer metastases in patients with a detectable serum thyroglobulin (especially serum thyroglobulin levels greater than 10 ng/mL and rising) who have a normal whole-body RAI scan and an unrevealing neck ultrasound. It is also sensitive for detecting metastases from medullary thyroid carcinoma. Diabetic patients with serum glucose less than 200 mg/dL (11.2 mmol/L) may be scanned, since the tracer acts like glucose in the body. ¹⁸FDG-PET scanning can be combined with a CT scan; the resultant ¹⁸FDG-PET/CT fusion scan is 60% sensitive for detecting metastases that are not visible by other methods. This scan is less sensitive for small brain metastases. ¹⁸FDG-PET scanning detects the metabolic activity of tumor tissue; for differentiated thyroid carcinoma, this scan is more sensitive when the patient's thyroid cancer is stimulated with rhTSH (Thyrogen) (see Recombinant human TSH [rhTSH]-stimulated ¹³¹I therapy above). ¹⁸FDG-PET scanning, however, lacks specificity. False-positives can occur with benign hepatic tumors, sarcoidosis, radiation therapy, suture granulomas, reactive lymph nodes, or inflammation at surgical sites that can persist for months.

⁶⁸Ga-DOTATATE-PET scanning is useful for staging patients with medullary thyroid carcinoma. It is also useful to determine whether a patient can be treated with PRRT.

6. Other scanning—Thallium-201 (²⁰¹Tl) scans may be useful for detecting metastatic differentiated thyroid carcinoma when the ¹³¹I scan is normal but serum thyroglobulin is elevated. MRI scanning is particularly useful for imaging metastases in the brain, mediastinum, or bones.

CT scanning is useful for imaging and monitoring pulmonary metastases.

► Prognosis

1. Papillary thyroid carcinoma—This cancer has an overall mortality rate of 3%. It is best staged using the MACIS (metastasis, age, completeness of resection, invasion, size) scoring system (Table 26–8). ¹⁸FDG-PET scanning independently predicts survival, with patients having few PET-avid metastases and low SUV_{max} (highest image-pixel standardized uptake value) having a generally good prognosis, particularly for adults under age 45 years. Unlike other forms of cancer, patients with papillary thyroid carcinoma who have palpable lymph node metastases do not have a particularly increased mortality rate; however, their risk of local recurrence is increased. The following characteristics imply a worse prognosis: age over 45 years, male sex, bone or brain metastases, macronodular (greater than 1 cm) pulmonary metastases, and lack of ¹³¹I uptake into metastases. The papillary histologic types of tall cell, columnar cell, and diffuse sclerosing types are associated with a higher risk of recurrence and reduced survival. The best prognosis has been with the follicular variant of papillary thyroid cancer. Younger patients with pulmonary metastases tend to respond better to ¹³¹I therapy than do older adults. Brain metastases are detected in 1%; they reduce median survival to 12 months, but the patient's prognosis is improved by surgical resection.

2. Follicular thyroid carcinoma—The mortality rate of follicular thyroid carcinoma is 3.4 times higher than that of papillary carcinoma. The Hürthle cell variant of follicular carcinoma is even more aggressive. Both follicular carcinoma and its Hürthle cell variant tend to present at a more advanced stage than papillary carcinoma. However, at a given stage, the different types of differentiated thyroid carcinoma have a similar prognosis. Patients with primary tumors larger than 1 cm who undergo limited thyroid surgery (subtotal thyroidectomy or lobectomy) have a 2.2-fold increased mortality over those having total or near-total thyroidectomies. Patients who have not received ¹³¹I ablation have mortality rates that are increased twofold by 10 years and threefold by 25 years (over those who have received ablation). The risk of cancer recurrence is twofold higher in men than in women and 1.7-fold higher in multifocal than in unifocal tumors.

Patients with a normal ¹⁸FDG-PET scan have a 98% 5-year survival, while those having more than 10 metastases have a 20% 5-year survival. Those with a SUV_{max} of 0.1–4.6 have a 5-year survival of 85%, while those with a SUV_{max} greater than 13.3 have a 5-year survival of 20%. Patients with only local metastases have a 5-year survival of 95%, while those with regional (supravacular, mediastinal) metastases have a 5-year survival of 70%, and those with distant metastases have a 5-year survival of 35%.

3. Medullary thyroid carcinoma—This cancer is more aggressive than differentiated thyroid cancer but is typically fairly indolent. However, medullary thyroid carcinoma with a somatic RET codon M918T mutation is the

most aggressive medullary thyroid carcinoma and has a poorer prognosis. The overall 10-year survival rate is 90% when the tumor is confined to the thyroid, 70% for those with metastases to cervical lymph nodes, and 20% for those with distant metastases. When postoperative serum calcitonin levels are below 150 pg/mL (44 pmol/L), residual disease is likely confined to the neck, whereas when postoperative serum calcitonin levels are above 500 pg/mL (146 pmol/L), distant metastases are likely. Patients with metastatic medullary thyroid carcinoma whose serum calcitonin doubling time is over 2 years also have a relatively good prognosis.

4. Other thyroid carcinomas—Anaplastic thyroid carcinoma carries a 1-year survival rate of about 10% and a 5-year survival rate of about 5%. Patients with fully localized tumors on MRI have a better prognosis.

Localized thyroid lymphoma carries a 5-year survival of nearly 100%. Those with disease outside the thyroid have a 63% 5-year survival. However, the prognosis is better for those with mucosa-associated lymphoid tissue lymphoma compared to diffuse large B-cell lymphoma. Patients presenting with stridor, pain, laryngeal nerve palsy, or mediastinal extension tend to fare worse.

Ciarallo A et al. Radioactive iodine therapy in differentiated thyroid cancer: 2020 update. *AJR Am J Roentgenol*. 2020; 215:285. [PMID: 32551904]

Leenhardt L et al. Recombinant thyrotropin vs levothyroxine withdrawal in ^{131}I therapy of N1 thyroid cancer: a large matched cohort study (ThyrNod). *J Clin Endocrinol Metab*. 2019;104:1020. [PMID: 30398518]

Tiedje V et al. Therapeutic breakthroughs for metastatic thyroid cancer. *Nat Rev Endocrinol*. 2020;16:77. [PMID: 31819229]

Zhang C et al. Total thyroidectomy versus lobectomy for papillary thyroid cancer: a systematic review and meta-analysis. *Medicine (Baltimore)*. 2020;99:e19073. [PMID: 32028431]

IODINE DEFICIENCY DISORDER & ENDEMIC GOITER

ESSENTIALS OF DIAGNOSIS

- ▶ Common in regions with low-iodine diets.
- ▶ High rate of congenital hypothyroidism and cretinism.
- ▶ Goiters may become multinodular and enlarge.
- ▶ Most adults with endemic goiter are euthyroid; however, some are hypothyroid or hyperthyroid.

General Considerations

Moderate iodine deficiency during gestation and infancy can cause manifestations of hypothyroidism, deafness, and short stature and can lower a child's intelligence quotient by 10–15 points. Even mild-to-moderate iodine deficiency appears to impair a child's perceptual reasoning and global cognitive index. Severe iodine deficiency increases the risk

of miscarriage and stillbirth. Cretinism occurs in about 0.5% of live births in iodine-deficient areas.

Although iodine deficiency is the most common cause of endemic goiter, there are other natural goitrogens, including certain foods (eg, sorghum, millet, maize, cassava), mineral deficiencies (selenium, iron, zinc), and water pollutants, which can themselves cause goiter or aggravate a goiter proclivity caused by iodine deficiency. In iodine-deficient patients, cigarette smoking can induce goiter growth. Pregnancy aggravates iodine deficiency. Some individuals are particularly susceptible to goiter owing to congenital partial defects in thyroid enzyme activity.

Clinical Findings

A. Symptoms and Signs

Endemic goiters may become multinodular and very large. Growth often occurs during pregnancy, increasing the size of thyroid nodules and causing new nodules; compressive symptoms may occur.

Substernal goiters are usually asymptomatic but can cause tracheal compression, respiratory distress, dysphagia, superior vena cava syndrome, gastrointestinal bleeding from esophageal varices, palsies of the phrenic or recurrent laryngeal nerves, or Horner syndrome. Cerebral ischemia and stroke can result from arterial compression or thyrocervical steal syndrome. Substernal goiters can rarely cause pleural or pericardial effusions. The incidence of significant malignancy is less than 1%.

Some patients with endemic goiter may become hypothyroid. Others may become thyrotoxic as the goiter grows and becomes more autonomous, especially if iodine is added to the diet.

B. Laboratory Findings

The serum T_4 and TSH are generally normal. TSH is low in hyperthyroidism if a multinodular goiter has become autonomous and there is sufficient amounts of iodine for thyroid hormone synthesis. TSH increases with hypothyroidism. Thyroid RAI uptake is usually elevated, but it may be normal if iodine intake has improved. Serum antithyroid antibodies are usually either undetectable or in low titers. Serum thyroglobulin is often elevated above 13 mcg/L. Urine iodine concentrations are low.

Differential Diagnosis

Endemic goiter must be distinguished from other forms of nodular goiter that may coexist in an endemic region.

Prevention

The daily minimum dietary requirement for iodine is 150 mcg daily in nonpregnant adults and 250 mcg daily for pregnant or lactating women. Iodized salt contains iodine at about 20 mg per kg salt. Other sources of iodine include commercial bread, milk, and seafood. Initiating iodine supplementation in an iodine-deficient area greatly reduces the emergence of new goiters but causes an increased frequency of hyperthyroidism during the first year.

► Treatment

Iodine supplementation has not proven effective for treating adults with large multinodular goiter due to iodine deficiency and actually increases their risk of developing thyrotoxicosis. Thyroidectomy may be required for cosmesis, compressive symptoms, or thyrotoxicosis. There is a high goiter recurrence rate in iodine-deficient geographic areas, so near-total thyroidectomy is preferred when surgery is indicated. Certain patients may be treated with ^{131}I for large compressive goiters.

► Complications

Dietary iodine supplementation increases the risk of autoimmune thyroid dysfunction, which may cause hypothyroidism or hyperthyroidism. Excessive iodine supplementation increases the risk of goiter. Suppression of TSH by administering levothyroxine carries the risk of inducing hyperthyroidism, particularly in patients with autonomous multinodular goiters; levothyroxine suppression should not be started in patients with a low TSH level. Treating patients with ^{131}I for large multinodular goiter may shrink the gland; however, Graves disease develops in some patients 3–10 months following therapy.

Dineva M et al. Systematic review and meta-analysis of the effects of iodine supplementation on thyroid function and child neurodevelopment in mildly-to-moderately iodine deficient pregnant women. Am J Clin Nutr. 2020;112:389. [PMID: 32320029]

▼ DISEASES OF THE PARATHYROIDS

HYPOPARATHYROIDISM & PSEUDOHYPOPARATHYROIDISM



ESSENTIALS OF DIAGNOSIS

- ▶ Tetany, carpopedal spasms, tingling of lips and hands, muscle cramps, irritability.
- ▶ Chvostek sign and Trousseau phenomenon.
- ▶ Hypocalcemia with low serum PTH; serum phosphate high; alkaline phosphatase normal; urine calcium excretion reduced.
- ▶ Serum magnesium may be low.

► General Considerations

Acquired hypoparathyroidism is most commonly caused by anterior neck surgery, occurring after total thyroidectomy in about 25% of patients transiently, and in about 4% of patients permanently. The risk of permanent postoperative hypoparathyroidism can be reduced during thyroid surgery by taking parathyroid glands with suspected vascular damage and autotransplanting them into the sternocleidomastoid muscle. Permanent hypoparathyroidism may occur after the resection of multiple parathyroid adenomas. It also

occurs transiently after the surgical removal of a single parathyroid adenoma for primary hyperparathyroidism due to suppression of the remaining normal parathyroids and accelerated remineralization of the skeleton. This is known as “hungry bone syndrome.” In such cases, hypocalcemia can be quite severe, particularly in patients with preoperative hyperparathyroid bone disease and vitamin D or magnesium deficiency. All patients undergoing thyroidectomy or parathyroidectomy must be observed closely overnight. Neck irradiation is a rare cause of hypoparathyroidism.

Autoimmune hypoparathyroidism may be isolated or combined with other endocrine deficiencies. Autoimmune polyendocrine syndrome type I (APS-I) is also known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED). Hypoparathyroidism can also occur in SLE caused by antiparathyroid antibodies.

Parathyroid deficiency may also be the result of damage from heavy metals such as copper (Wilson disease) or iron (hemochromatosis, transfusion hemosiderosis), granulomas, Riedel thyroiditis, tumors, or infection.

Magnesium deficiency causes functional hypoparathyroidism. Although mild hypomagnesemia stimulates PTH secretion, more profound hypomagnesemia (below 1.2 mg/dL) inhibits PTH secretion. Hypomagnesemia also causes resistance to PTH in bone and renal tubules. Correction of hypomagnesemia results in rapid disappearance of the condition.

Hypermagnesemia, likewise, suppresses PTH secretion.

Congenital hypoparathyroidism causes hypocalcemia beginning in infancy. However, it may not be diagnosed for many years. Since hypoparathyroidism can be familial, screening is suggested for family members of any patient with idiopathic hypoparathyroidism.

► Clinical Findings

A. Symptoms and Signs

Symptoms of hypoparathyroidism depend on the severity and rate of development of hypocalcemia as well as individual factors. Patients with acute hypocalcemia after parathyroidectomy may manifest severe symptoms, despite having only mildly low or even low-normal serum calcium levels. Patients with chronic severe hypocalcemia may have few symptoms. **Neuromuscular irritability** presents with perioral numbness, paresthesias of the feet or hands, myalgias, muscle cramping, generalized muscle spasms with tetany, hyperactive reflexes, and laryngospasm that can cause respiratory stridor. Chvostek sign (facial muscle contraction on tapping the facial nerve in front of the tragus) is present in 70% of patients with hypocalcemia and in about 15% of individuals who are normocalcemic. Trousseau sign (flexion of the wrist and metacarpal-phalangeal joints with adduction of the fingers after application of a sphygmomanometer cuff inflated to over systolic blood pressure for 3 minutes) is present in over 90% of patients with hypocalcemia but in only about 1% of normocalcemic individuals. **Cardiovascular** manifestations of acute hypocalcemia include bradycardia, ventricular arrhythmias, and impaired ventricular ejection fraction. **CNS** manifestations include seizures as well as psychiatric changes, irritability, fatigue, and cognitive

impairment. Parkinsonian and extrapyramidal symptoms may occur. **Ophthalmic** manifestations of severe hypocalcemia include papilledema and cataracts. **Renal** manifestations of chronic hypoparathyroidism occur due to hypercalciuria and include nephrolithiasis, nephrocalcinosis, and kidney disease. **Dermatologic** manifestations include dry, rough skin; dry hair; scalp and eyebrow hair loss; and brittle fingernails with transverse grooves. Chronic hypocalcemia with hyperphosphatemia can cause calcifications in soft tissues, such as joints, skin, and arteries.

B. Laboratory Findings

Serum calcium is low, serum phosphate high, urinary calcium low, and alkaline phosphatase normal. Serum calcium is largely bound to albumin. In patients with hypoalbuminemia, the serum ionized calcium may be determined; it should be 4.6–5.3 mg/dL (1.15–1.32 mmol/L). Alternatively, the serum calcium level can be corrected for serum albumin level as follows:

$$\text{"Corrected" serum Ca}^{2+} = \text{Serum Ca}^{2+} \text{ mg/dL} + (0.8 \times [4.0 - \text{Albumin g/dL}])$$

Serum PTH levels are usually low or not elevated in the presence of hypocalcemia. Serum magnesium levels should always be measured. Serum calcium should not be determined within 24 hours following intravenous gadolinium, since gadolinium interferes with the colorimetric calcium assay, thereby causing artefactual hypocalcemia.

C. Imaging

Brain calcifications are visible on CT scanning in the basal ganglia and other areas in over 50% of patients with chronic hypocalcemia. The bones may appear denser than normal and the bone mineral density (BMD) is usually increased, particularly in the lumbar spine. Cutaneous calcification may occur.

D. Other Examinations

Slit-lamp examination may show early posterior lenticular cataract formation. The electrocardiogram (ECG) may show heart block, a prolonged QTc interval, and ST-T changes suggestive of a myocardial infarction.

Complications

Acute tetany with stridor, especially if associated with vocal cord palsy, may lead to respiratory obstruction requiring tracheostomy. Seizures are common in untreated patients. Hypocalcemia can also cause heart failure and dysrhythmias. Ossification of the paravertebral ligaments may occur with nerve root compression; surgical decompression may be required. Overtreatment with vitamin D and calcium may produce nephrocalcinosis and impairment of kidney function. There may be associated autoimmunity causing celiac disease, pernicious anemia, or Addison disease.

Differential Diagnosis

Paresthesias, muscle cramps, or tetany due to respiratory alkalosis, in which the serum calcium is normal, can be

confused with hypocalcemia. In fact, hyperventilation tends to accentuate hypocalcemic symptoms.

Hypocalcemia may be caused by certain drugs: loop diuretics, plicamycin, phenytoin, foscarnet, denosumab, and bisphosphonates. In addition, hypocalcemia may be seen in cases of rapid intravascular volume expansion or due to chelation from transfusions of large volumes of citrated blood. Hypocalcemia may also be due to malabsorption of calcium, magnesium, or vitamin D; patients do not always have diarrhea. It is also observed in patients with acute pancreatitis. Hypocalcemia may develop in patients with osteoblastic metastatic carcinomas (especially breast, prostate) instead of the expected hypercalcemia. Hypocalcemia with hyperphosphatemia (simulating hypoparathyroidism) is seen in azotemia, but may also be caused by large doses of intravenous, oral, or rectal phosphate preparations and by chemotherapy of responsive lymphomas or leukemias.

Hypocalcemia with hypercalciuria may be due to a familial autosomal dominant syndrome involving a mutation in the calcium-sensing receptor; patients have serum PTH levels that are in the normal range, distinguishing it from hypoparathyroidism. Such patients are hypercalcemic; treatment with calcium and vitamin D may cause nephrocalcinosis.

Congenital pseudohypoparathyroidism is a group of disorders characterized by hypocalcemia due to resistance to PTH. Subtypes are caused by different mutations involving the renal PTH receptor, the receptor's G protein, or adenylyl cyclase.

Treatment

A. Prophylaxis Against Severe Postoperative Hypocalcemia

Post-thyroidectomy hypocalcemia can be detected early by closely monitoring serum PTH and calcium. If the serum calcium falls below 8.0 mg/dL (2.0 mmol/L) with a serum PTH below 10–15 pg/mL (1.0–1.5 pmol/L) after thyroid or parathyroid surgery, the patient is at high risk for hypocalcemia and can be prophylactically treated with calcitriol and calcium. An oral prophylactic regimen is calcitriol, 0.25–1 mcg twice daily, and calcium carbonate (with meals), 500–1000 mg twice daily.

B. Emergency Treatment for Acute Hypocalcemia (Hypoparathyroid Tetany)

1. Airway—Be sure an adequate airway is present.

2. Intravenous calcium gluconate—Calcium gluconate, 10–20 mL of 10% solution intravenously, may be given slowly until tetany ceases. Ten to 50 mL of 10% calcium gluconate may be added to 1 L of 5% glucose in water or saline and administered by slow intravenous drip. The rate should be adjusted so that the serum calcium is maintained in the range of 8–9 mg/dL (2–2.25 mmol/L).

3. Oral calcium—Oral calcium salts should be given as soon as possible to supply 1–2 g of elemental calcium daily. Liquid calcium carbonate, 500 mg/5 mL, contains 40% calcium and may be especially useful; it should be given with meals.

4. Vitamin D preparations—(Table 26–9) Vitamin D therapy should be started as soon as oral calcium is begun. 1,25-Dihydroxycholecalciferol (calcitriol) has a very rapid onset of action and is not as long-lasting as vitamin D₃ if hypercalcemia occurs. Begin calcitriol at a dose of 0.25 mcg (1000 international units) orally each morning and titrate upward to near normocalcemia. Ultimately, doses of 0.5–4 mcg/day may be required.

5. Magnesium—If hypomagnesemia (serum magnesium less than 1.8 mg/dL or less than 0.8 mmol/L) is present, it must be corrected to treat the resulting hypocalcemia. For critical hypomagnesemia (serum magnesium less than 1.0 mg/dL or less than 0.45 mmol/L), 50% magnesium sulfate solution (5 g/10 mL) is diluted in 250 mL 0.9% saline or 5% dextrose in water and given by an intravenous infusion of 5 g over 3 hours, with further dosing based on serum magnesium levels. Long-term oral magnesium replacement may be given as magnesium oxide 500 mg (60% elemental magnesium) tablets, one to three times daily.

C. Maintenance Treatment of Hypoparathyroidism

Patients with mild hypoparathyroidism may require no therapy but need close monitoring for manifestations of hypocalcemia. Therapy is ordinarily required for symptomatic hypocalcemia or serum calcium below 8.0 mg/dL (2 mmol/L).

Vitamin D, calcium, and magnesium therapy: Patients with hypoparathyroidism have a reduced renal tubular reabsorption of calcium and are thus prone to hypercalcuria and kidney stones if the serum calcium is normalized with calcium and vitamin D therapy. Therefore, the goal is to maintain the serum calcium in a slightly low but asymptomatic range of 8–8.6 mg/dL (2–2.15 mmol/L). It is prudent to monitor urine calcium with “spot” urine determinations and keep the level below 30 mg/dL (7.5 mmol/L), if possible. Hypercalcuria may respond to oral hydrochlorothiazide, 25 mg daily, usually given with a potassium supplement. Serum magnesium should be monitored and kept in the normal range with supplemental

magnesium, if required. Serum phosphate should also be monitored and the serum calcium × phosphate product kept below 55 mg²/dL² (4.4 mmol²/L²).

Calcium supplements can be given in doses of 800–1000 mg orally daily. Calcium carbonate (40% elemental calcium) is best absorbed at the low gastric pH that occurs with meals. Calcium citrate (21% elemental calcium) is absorbed with or without meals and is a better choice for patients taking proton pump inhibitors or H₂-blockers; it causes less gastrointestinal intolerance than calcium carbonate. Calcium supplements are given orally in divided doses to provide 800–1200 mg elemental calcium daily.

Vitamin D analogs are generally required for patients with chronic hypoparathyroidism (Table 26–9). The dosage of vitamin D preparations required to maintain target serum calcium levels can vary over time. In hypoparathyroidism, there is a deficiency in renal 1-hydroxylation of vitamin D therefore, vitamin D analogs that are already 1-hydroxylated (activated) (such as calcitriol and alfacalcidol) are usually used. Monitoring serum calcium, serum phosphate, and serum 25-(OH) vitamin D levels is recommended at least every 3–4 months. Vitamin D₃ may be required in doses of 1000–5000 units daily to maintain serum 25-(OH) vitamin D above 30 ng/mL.

For patients with recurrent hypocalcemia despite treatment with active vitamin D analogs, the use of cholecalciferol (vitamin D₃, derived from skin exposed to sunlight or diet supplements) or ergocalciferol (vitamin D₂, derived from plants) is a treatment option (Table 26–9). These vitamin D preparations have a biologic duration of action of 4–6 weeks; if hypercalcemia develops, it may persist for weeks after the preparation is discontinued. Severe hypercalcemia requires treatment with hydration and prednisone. Despite the risk of prolonged hypercalcemia, cholecalciferol and ergocalciferol usually produce more stable serum calcium levels than the shorter-acting preparations.

PTH is effectively treats patients with hypoparathyroidism but is restricted to patients whose hypocalcemia cannot be adequately treated with calcium and vitamin D

Table 26–9. Vitamin D preparations used in the treatment of hypoparathyroidism.

	Available Preparations	Daily Dose	Duration of Action
Calcitriol (Rocaltrol)	0.25 mcg (1000 international units) and 0.5 mcg (2000 international units) capsules; 1 mcg/mL oral solution; 1 mcg/mL for injection	0.25–3 mcg divided into 2 doses daily	3–5 days
Alfacalcidol	0.25 mcg, 0.5 mcg, and 1 mcg capsules	0.25 mcg with calcitriol, 0.5–3.0 mcg (divided into 2 doses) without calcitriol	3–5 days
Cholecalciferol (vitamin D ₃)	400 international units/mL liquid, 1000–50,000 international units capsules (not available commercially in United States; may be compounded)	400–4000 international units with calcitriol, 10,000–100,000 units without calcitriol	4–8 weeks
Ergocalciferol, ergosterol (vitamin D ₂ , calciferol)	8000 international units/mL liquid, 50,000 international units capsules	400–4000 international units with calcitriol, 50,000–200,000 international units without calcitriol	1–2 weeks

analogs. Recombinant human parathyroid hormone (rhPTH) is identical to native PTH. It is FDA approved and marketed as NATPARA as an adjunct to calcium and vitamin D analogs to control symptomatic hypocalcemia in patients with hypoparathyroidism. It must be given by subcutaneous injection every 1–2 days. Side effects of rhPTH include nausea, vomiting, diarrhea, arthralgias, and paresthesias. Also, osteosarcoma has occurred in rats receiving very high-dose PTH. The FDA requires that prescribers be certified before prescribing the drug and that patients and prescribers formally acknowledge the risk of osteosarcoma. The expense of rhPTH limits its use.

Transplantation of cryopreserved parathyroid tissue, removed during prior surgery, restores normocalcemia in about 23% of cases.

Hypoparathyroidism in pregnancy presents special challenges. Maternal hypocalcemia can adversely affect the skeletal development of the fetus and cause compensatory hyperparathyroidism in the newborn. Maternal hypercalcemia can suppress fetal parathyroid development, resulting in neonatal hypocalcemia. This requires very close clinical and biochemical monitoring during pregnancy.

Caution: Phenothiazine drugs should be administered with caution, since they may precipitate extrapyramidal symptoms in hypocalcemic patients. Furosemide should be avoided, since it may worsen hypocalcemia.

► Prognosis

Patients with mild hypoparathyroidism generally do well. Periodic serum calcium levels are required, since changes may call for modification of the treatment schedule. Hypercalcemia that develops in patients with seemingly stable, treated hypoparathyroidism may be a presenting sign of Addison disease.

Despite optimal therapy, patients with moderate-to-severe hypoparathyroidism have an overall reduced quality of life. Chronically affected patients frequently develop calcifications in their kidneys and basal ganglia. They have an increased risk of calcium kidney stones and kidney dysfunction as well as seizures, mood and psychiatric disorders, and a reduced overall sense of well-being. Therapy with rhPTH may prevent or improve these manifestations.

Bilezikian JP. Hypoparathyroidism. *J Clin Endocrinol Metab*. 2020;105:1722. [PMID: 32322899]
Gafni RI et al. Hypoparathyroidism. *N Engl J Med*. 2019;380:1738. [PMID: 31042826]

HYPERPARATHYROIDISM



ESSENTIALS OF DIAGNOSIS

- Often found incidentally by routine blood testing.
- Renal calculi, polyuria, hypertension, constipation, fatigue, mental changes.
- Bone pain; rarely, cystic lesions and pathologic fractures.

- Elevated serum PTH, serum and urine calcium, and urine phosphate; serum phosphate low to normal; alkaline phosphatase normal to elevated.

► General Considerations

Primary hyperparathyroidism is the most common cause of hypercalcemia, with an estimated prevalence of 0.89% of the population in the United States. However, it is widely underdiagnosed and undertreated. It occurs at all ages but most commonly in the seventh decade and in women (74%). Before age 45, the prevalence is similar in men and women. It is more prevalent in Blacks, followed by Whites, then other races.

Parathyroid glands vary in number and location and ectopic parathyroid glands have been found within the thyroid gland, high in the neck or carotid sheath, in the retroesophageal space, and within the thymus or mediastinum. Hyperparathyroidism is caused by hypersecretion of PTH, usually by a single parathyroid adenoma (80%), and less commonly by hyperplasia or adenomas of two or more parathyroid glands (20%), or carcinoma (less than 1%). However, when hyperparathyroidism presents before age 30 years, there is a higher incidence of multiglandular disease (36%) and parathyroid carcinoma (5%). The size of the parathyroid adenoma correlates with the serum PTH level.

Hyperparathyroidism is familial in about 5–10% of cases; hyperparathyroidism presenting before age 45 has a higher chance of being familial. Parathyroid hyperplasia commonly arises in MEN types 1, 2 (2A), and 4. (See Table 26–12.)

Hyperparathyroidism results in the excessive excretion of calcium and phosphate by the kidneys. PTH stimulates renal tubular reabsorption of calcium; however, hyperparathyroidism causes hypercalcemia and an increase in calcium in the glomerular filtrate that overwhelms tubular reabsorption capacity, resulting in hypercalciuria. At least 5% of renal calculi are associated with this disease. Diffuse parenchymal calcification (nephrocalcinosis) is seen less commonly.

Parathyroid carcinoma is a rare cause of hyperparathyroidism, accounting for less than 1% of hyperparathyroidism. Local recurrence is the rule if surgical margins are positive. Distant metastases arise most commonly in the lungs but also in bones, liver, brain, and mediastinum. Although parathyroid carcinoma is typically indolent, an increasing tumor burden is associated with critically severe hypercalcemia and death.

Secondary and tertiary hyperparathyroidism usually occurs with chronic kidney disease, in which hyperphosphatemia and decreased renal production of 1,25-dihydroxycholecalciferol ($1,25[\text{OH}]_2\text{D}_3$) initially produce a decrease in ionized calcium. The parathyroid glands are stimulated (secondary hyperparathyroidism) and may enlarge, becoming autonomous (tertiary hyperparathyroidism). Renal osteodystrophy is the bone disease of this disorder (see Disorders of Mineral Metabolism, Chapter 22). Secondary hyperparathyroidism predictably develops in

patients with a deficiency in vitamin D. Serum calcium levels are typically in the normal range, but may rise to become borderline elevated with time, with tertiary hyperparathyroidism due to parathyroid glandular hyperplasia.

► Clinical Findings

A. Symptoms and Signs

In the developed world, hypercalcemia is typically discovered incidentally by routine chemistry panels. Many patients are asymptomatic or have mild symptoms that may be elicited only upon questioning. Parathyroid adenomas are usually so small and deeply located in the neck that they are almost never palpable; when a mass is palpated, it usually turns out to be an incidental thyroid nodule.

Symptomatic patients are said to have problems with “bones, stones, abdominal groans, psychic moans, with fatigue overtones.”

1. Skeletal manifestations—Low bone density is typically most prominent at the distal one-third of the radius, a site of mostly cortical bone. Lumbar (trabecular) spine bone density is often spared and is higher compared to the distal radius. Hip bones are a mixture of trabecular and cortical bone, and femur bone density tends to be midway between the lumbar spine and distal radius. Postmenopausal women are prone to asymptomatic vertebral fractures, but severe bone demineralization is uncommon in mild hyperparathyroidism. More commonly, patients experience arthralgias and bone pain, particularly involving the legs. Severe chronic hyperparathyroidism can cause **osteitis fibrosa cystica**, which is the replacement of calcified bone matrix with fibrous tissue forming cystic brown tumors of bone that can be palpable in the jaw.

2. Hypercalcemic manifestations—Mild hypercalcemia may be asymptomatic. However, hypercalcemia usually causes symptoms whose severity is not entirely predictable by the level of serum calcium or PTH; patients with mild hypercalcemia can have significant symptoms, particularly depression, constipation, and bone and joint pain. **Neuromuscular** manifestations include paresthesias, muscle cramps and weakness, and diminished deep tendon reflexes. **Neuropsychiatric** manifestations include malaise, headache, fatigue, insomnia, irritability, and depression. Patients may have cognitive impairment that can vary from intellectual weariness to severe disorientation, psychosis, or stupor. **Cardiovascular** manifestations include hypertension, palpitations, prolonged P-R interval, shortened Q-T interval, bradyarrhythmias, heart block, asystole, and sensitivity to digitalis. Overall cardiovascular mortality is increased in patients with chronic moderate to severe hypercalcemia. **Renal** manifestations include polyuria and polydipsia from hypercalcemia-induced nephrogenic diabetes insipidus. Among all patients with newly discovered hyperparathyroidism, calcium-containing renal calculi have occurred or are detectable in about 18%. Patients with asymptomatic hyperparathyroidism have a 5% incidence of asymptomatic calcium nephrolithiasis, compared to 1.6% incidence in age-matched controls. **Gastrointestinal** symptoms include anorexia, nausea, heartburn, vomiting,

abdominal pain, weight loss, constipation, and obstipation. Pancreatitis occurs in 3%. **Dermatologic** symptoms may include pruritus. Calcium may precipitate in the corneas (“band keratopathy”), in extravascular tissues (calcinosis), and in small arteries, causing small vessel thrombosis and skin necrosis (calciphylaxis).

3. Normocalcemic primary hyperparathyroidism

Patients with normocalcemic primary hyperparathyroidism generally have few symptoms. However, on average, such patients have a slightly more atherogenic lipid panel and higher blood pressures (systolic blood pressure 10 mm Hg higher and diastolic blood pressure 7 mm Hg higher) than controls. Also, affected patients can have very subtle symptoms, such as mild fatigue, that may not be appreciated as abnormal.

4. Hyperparathyroidism during pregnancy

Pregnant women having mild hyperparathyroidism with a serum calcium below 11.0 mg/dL (less than 2.75 mmol/L) generally tolerate pregnancy well with normal outcomes. However, the majority of pregnant women with more severe hypercalcemia experience complications such as nephrolithiasis, hyperemesis, pancreatitis, muscle weakness, and cognitive changes. About 30% of affected women experience preeclampsia and two-thirds of eclamptic women have preterm delivery. Hypercalcemic crisis may occur, especially postpartum. About 80% of fetuses experience complications of maternal hyperparathyroidism, including fetal demise, preterm delivery, and low birth weight. Newborns have hypoparathyroidism that can be permanent.

5. Parathyroid carcinoma

Hyperparathyroidism with a large palpable neck mass, or vocal fold paralysis from recurrent laryngeal nerve palsy, raises concern for parathyroid carcinoma. Some cases present with smaller tumors, less severe hypercalcemia, and benign-appearing histologic features. *FNA biopsy is not recommended because it may seed the biopsy tract with tumor and cytologic distinction between benign and malignant tumors is problematic.* Parathyroid carcinoma is more frequent in patients with hyperparathyroidism-jaw tumor syndrome as well as patients with MEN 1 and MEN 2A. Therefore, patients should have genetic testing.

B. Laboratory Findings

The hallmark of primary hyperparathyroidism is hypercalcemia, with the serum adjusted total calcium greater than 10.5 mg/dL (2.6 mmol/L). The adjusted total calcium = measured serum calcium in mg/dL + [0.8 × (4.0 – patient's serum albumin in g/dL)]. Serum ionized calcium levels are elevated (above 1.36 mmol/L).

To confirm the diagnosis of hyperparathyroidism, assess urinary calcium excretion, particularly for patients with mild hyperthyroidism. In primary hyperparathyroidism, the urine calcium excretion is normal (100–300 mg/day [25–75 mmol/day]) or high. Low urine calcium excretions (below 100 mg/day [25 mmol/day]) in the absence of thiazide diuretics occur in only 4% of cases of primary hyperthyroidism and raise the differential diagnosis of familial hypocalciuric hypercalcemia.

The serum phosphate is often less than 2.5 mg/dL (0.8 mmol/L). In primary hyperparathyroidism, there is an excessive loss of phosphate in the urine in the presence of hypophosphatemia (25% of cases). A serum calcium:phosphate (Ca/P) ratio above 2.5 (mg/dL) or above 2.17 (mmol/L) helps confirm the diagnosis of primary hyperparathyroidism. The alkaline phosphatase is elevated only if bone disease is present. The plasma chloride and uric acid levels may be elevated. Vitamin D deficiency is common in patients with hyperparathyroidism; screen for vitamin D deficiency with a serum 25-OH vitamin D determination. Serum 25-OH vitamin D levels below 20 mcg/L (50 nmol/L) can aggravate hyperparathyroidism and its bone manifestations.

Elevated serum levels of intact PTH confirm the diagnosis of hyperparathyroidism. Parathyroid carcinoma must always be suspected in patients with a serum calcium of 14.0 mcg/dL (3.5 mmol/L) or more and a serum PTH 5 or more times the upper limit of normal.

Patients with low bone density and an elevated serum PTH but with a normal serum calcium must be evaluated for causes of secondary hyperparathyroidism (eg, vitamin D or calcium deficiency, hyperphosphatemia, chronic kidney disease). In the absence of secondary hyperparathyroidism, patients with an elevated serum PTH but normal serum calcium have **normocalcemic hyperparathyroidism**. Such individuals require monitoring, since hypercalcemia develops in about 19% of patients over 3 years of follow-up.

Genetic testing is recommended for patients with documented primary hyperparathyroidism who are younger than age 40 or who have multiglandular disease or a family history of hyperparathyroidism.

C. Imaging

Parathyroid imaging is not necessary for the diagnosis of hyperparathyroidism. Imaging is performed for most patients prior to parathyroid surgery.

Ultrasound of the neck should scan the neck from the mandible to the superior mediastinum in an effort to locate ectopic parathyroid adenomas. Ultrasound has a sensitivity of 79% for single adenomas but only 35% for multiglandular disease.

Sestamibi scintigraphy with ^{99m}Tc -sestamibi and single-photon emission computed tomography (SPECT) is most useful for localizing parathyroid adenomas. However, false-positive scans are common, caused by thyroid nodules, thyroiditis, or cervical lymphadenopathy. Sestamibi-SPECT imaging improves sensitivity for single parathyroid adenomas. Small benign thyroid nodules are discovered incidentally in nearly 50% of patients with hyperparathyroidism who have imaging with ultrasound or MRI.

^{18}F -fluorocholine PET/MRI is a useful scan for patients with primary hyperparathyroidism and negative or discordant localization imaging on neck ultrasound and sestamibi scanning. In a small study, the sensitivity of this scan was 90%, with a 100% positive predictive value.

Conventional CT and MRI imaging are not usually required prior to a first neck surgery for hyperparathyroidism. However, a four-dimensional CT (4D-CT), with the

fourth dimension referring to time, captures the rapid uptake and washout of contrast from parathyroid adenomas; it is particularly useful for preoperative imaging when ultrasonography and sestamibi scans are negative. It can also be helpful for patients who have had prior neck surgery and for those with ectopic parathyroid glands. In such patients, 4D-CT has a sensitivity of 88%, versus 54% for sestamibi SPECT and 21% for ultrasound. However, 4D-CT delivers more radiation to the thyroid and so is used mostly for older patients. MRI may also be useful for repeat neck operations and when ectopic parathyroid glands are suspected. MRI shows better soft tissue contrast than CT.

Noncontrast CT scanning of the kidneys in patients with hyperparathyroidism can visualize calcium-containing stones. However, for patients with mild and apparently asymptomatic hyperparathyroidism, only about 5% are found to have unsuspected nephrolithiasis.

Bone density measurements by dual energy x-ray absorptiometry (DXA) are helpful in determining the amount of cortical bone loss in patients with hyperparathyroidism. DXA should include three areas: distal radius (cortical), hip (cortical and trabecular), and lumbar vertebrae (trabecular). Vertebral bone density is usually not diminished in hyperparathyroidism.

► Complications

Pathologic long bone fractures are a complication of hyperparathyroidism. Urinary tract infection due to stone and obstruction may lead to kidney disease and uremia. If the serum calcium level rises rapidly, clouding of sensorium, kidney disease, and rapid precipitation of calcium throughout the soft tissues may occur (calciphylaxis). Peptic ulcer and pancreatitis may be intractable before surgery. Insulomas or gastrinomas may be associated, as well as pituitary tumors (MEN type 1). Pseudogout may complicate hyperparathyroidism both before and after surgical removal of tumors. Hypercalcemia during gestation produces neonatal hypocalcemia.

In tertiary hyperparathyroidism due to chronic kidney disease, high serum calcium and phosphate levels may cause calciphylaxis; calcification of arteries can result in painful ischemic necrosis of skin and gangrene, cardiac arrhythmias, and respiratory failure. The actual serum levels of calcium and phosphate have not correlated well with calciphylaxis, but a calcium (mg/dL) \times phosphate (mg/dL) product over 70 is usually present.

► Differential Diagnosis

Artefactual hypercalcemia is common, so a confirmatory serum calcium level should be drawn after an overnight fast along with a serum protein, albumin, and triglyceride while ensuring that the patient is well-hydrated. Hypercalcemia may be due to high serum protein concentrations; in the presence of very high or low serum albumin concentrations, an adjusted serum calcium or a serum ionized calcium is more dependable than the total serum calcium concentration. Hypercalcemia may also be seen with dehydration.

Hypercalcemia of malignancy occurs most frequently with breast, lung, pancreatic, uterine, and renal cell

carcinoma, and paraganglioma. Most of these tumors secrete PTH-related protein (PTHrP) that has structural homologies to PTH and causes bone resorption and hypercalcemia similar to those caused by PTH. Serum PTH levels are low or low-normal while serum PTHrP levels are elevated; phosphate is often low. Other tumors can secrete excessive 1,25(OH)₂ vitamin D₃, particularly lymphoproliferative and ovarian malignancies. Plasma cell myeloma causes hypercalcemia in older individuals. Other hematologic cancers associated with hypercalcemia include monocytic leukemia, T-cell leukemia and lymphoma, and Burkitt lymphoma. The clinical features of malignant hypercalcemia can closely simulate hyperparathyroidism.

Pseudohyperparathyroidism of pregnancy presents with hypercalcemia during pregnancy. It is caused by hypersensitivity of the breasts to PRL. The breasts become abnormally enlarged and secrete excessive amounts of PTHrP that causes hypercalcemia. Treatment with dopamine agonists reverses the hypercalcemia.

Sarcoidosis and other granulomatous disorders, such as tuberculosis, berylliosis, histoplasmosis, coccidiomycosis, leprosy, and foreign-body granuloma, can cause hypercalcemia. Sarcoid granulomas can secrete PTHrP, but granulomas secrete 1,25(OH)₂D₃ and serum levels of 1,25(OH)₂D₃ are usually elevated in the presence of hypercalcemia. However, in hypercalcemia with disseminated coccidiomycosis, serum 1,25(OH)₂D₃ levels may not be elevated. Serum PTH levels are usually low.

Excessive calcium or vitamin D ingestion can cause hypercalcemia, especially in patients who concurrently take thiazide diuretics, which reduce urinary calcium loss. Hypercalcemia is reversible following withdrawal of calcium and vitamin D supplements. In vitamin D intoxication, hypercalcemia may persist for several weeks. Serum levels of 25-hydroxycholecalciferol (25[OH]D₃) are helpful to confirm the diagnosis. A brief course of corticosteroid therapy may be necessary if hypercalcemia is severe.

Familial hypocalciuric hypercalcemia (FHH) is an uncommon autosomal dominant inherited disorder. Reduced function of the calcium-sensing receptor (CaSR) causes the parathyroid glands to falsely "sense" hypocalcemia and inappropriately release excessive amounts of PTH. The renal tubule CaSRs are also affected, causing hypocalciuria.

FHH can sometimes present with neonatal severe primary hyperparathyroidism. Adults with hypercalcemia due to FHH are either asymptomatic or have nonspecific complaints such as fatigue, weakness, or cognitive issues. Recurrent pancreatitis can occur.

FHH is characterized by a mildly elevated serum calcium that is usually below 11.0 mg/dL (2.75 mmol/L) and a low urine calcium excretion that is usually less than 50 mg/24 h (13 mmol/24 h). Serum PTH levels are usually normal or minimally elevated. Serum phosphate levels are normal. About 4% of patients with true hyperparathyroidism can have a low urine calcium (below 100 mg/day). Therefore, FHH is confirmed with genetic testing for FHH gene mutations. These patients do not normalize their hypercalcemia after subtotal parathyroid removal and should not be subjected to surgery. Cinacalcet, a calcimimetic, may be helpful.

Prolonged immobilization at bed rest commonly causes hypercalcemia, particularly in adolescents, critically ill patients, and patients with extensive Paget disease of bone. Hypercalcemia develops in about one-third of acutely ill patients being treated in intensive care units, particularly patients with acute kidney injury. Serum calcium elevations are typically mild but may reach 15 mg/dL (3.75 mmol/L). Serum PTH levels are usually slightly elevated, consistent with mild hyperparathyroidism but may be suppressed or normal.

Rare causes of hypercalcemia include untreated adrenal insufficiency. Modest hypercalcemia is occasionally seen in patients taking thiazide diuretics or lithium; the PTH level may be inappropriately nonsuppressed with hypercalcemia. Hyperthyroidism causes increased turnover of bone and occasional hypercalcemia. Bisphosphonates can increase serum calcium in 20% and serum PTH becomes high in 10%, mimicking hyperparathyroidism. Other causes of hypercalcemia are shown in Table 21–7.

Treatment

A. "Asymptomatic" Primary Hyperparathyroidism

Patients with normocalcemic or mild hyperparathyroidism should be considered "asymptomatic" only after very close questioning. Many patients may not realize they have subtle manifestations, such as cognitive slowing, having become accustomed to such symptoms over years. It is important to assess blood pressure, serum BUN and creatinine, and to determine the presence of nephrolithiasis or nephrocalcinosis by radiography, ultrasonography, or CT scan of the kidneys. Truly asymptomatic patients may be closely monitored and advised to keep active, avoid immobilization, and drink adequate fluids. For postmenopausal women with hyperparathyroidism, estrogen replacement therapy reduces serum calcium by an average of 0.75 mg/dL (0.19 mmol/L) and slightly improves bone density. For patients with hypercalciuria (more than 400 mg daily) or calcium nephrolithiasis, hydrochlorothiazide may be used in doses of 12.5–25 mg daily to reduce calciuria; however, serum calcium must be monitored carefully. Parathyroidectomy does not improve the bone density of patients with osteoporosis who have normocalcemia or normohormonal hyperparathyroidism.

Affected patients should avoid large doses of thiazide diuretics, vitamin A, and calcium-containing antacids or supplements. Serum calcium and albumin are checked at least twice yearly, kidney function and urine calcium once yearly, and three-site bone density (lumbar vertebrae, hip, and distal radius) every 2 years. Rising serum calcium should prompt further evaluation and determination of serum PTH levels.

If it is not clear whether a patient with primary hyperparathyroid is symptomatic, it is reasonable to consider a trial of medical therapy with cinacalcet.

B. Medical Measures

- 1. Fluids**—Hypercalcemia is treated with a large fluid intake unless contraindicated. Severe hypercalcemia

requires hospitalization and intensive hydration with intravenous saline.

2. CaSR activators—Cinacalcet is a calcimimetic agent that binds to sites of the parathyroid glands' extracellular CaSRs to increase the glands' affinity for extracellular calcium, thereby decreasing PTH secretion. Cinacalcet may be used as the initial therapy for patients with hyperparathyroidism or for failed surgical parathyroidectomy. For primary hyperparathyroidism with mild hypercalcemia, begin cinacalcet (15 mg orally [one-half of a 30-mg tablet]) and monitor the serum calcium weekly; increase the dose every 2 weeks if hypercalcemia persists until the patient becomes normocalcemic, which is successful in about 65% of sporadic cases and 80% of familial cases. Patients with parathyroid carcinoma and severe hypercalcemia are treated with cinacalcet in addition to the bisphosphonate, zoledronic acid. For parathyroid cancer, cinacalcet is administered in doses of 30 mg orally twice daily, increased progressively to 60 mg twice daily, then 90 mg twice daily to a maximum of 90 mg every 6–8 hours. Cinacalcet is usually well tolerated but may cause nausea and vomiting (11%), myalgia, or malaise. Cinacalcet does not usually correct hypercalciuria. Hypocalcemia has occurred, even at 30 mg/day. About 50% of azotemic patients with secondary or tertiary hyperparathyroidism have hypercalcemia that is resistant to vitamin D analogs; begin cinacalcet 30 mg orally daily to a maximum of 250 mg daily, with dosage adjustments to keep the serum PTH in the range of 150–300 pg/mL (15.8–31.6 pmol/L). Etelcalcetide also activates the parathyroid glands' CaSR and reduces hypercalcemia in dialysis patients; it is given intravenously at the end of hemodialysis sessions, thereby avoiding the gastrointestinal side effects of cinacalcet.

3. Bisphosphonates—Intravenous bisphosphonates are potent inhibitors of bone resorption and can temporarily treat the hypercalcemia of hyperparathyroidism. Pamidronate in doses of 30–90 mg (in 0.9% saline) is administered intravenously over 2–4 hours. Zoledronic acid 5 mg is administered intravenously over 15–20 minutes. These drugs cause a gradual decline in serum calcium over several days that may last for weeks to months. Such intravenous bisphosphonates are used generally for patients with severe hyperparathyroidism in preparation for surgery. Oral bisphosphonates, such as alendronate, are not effective for treating the hypercalcemia or hypercalciuria of hyperparathyroidism. However, oral alendronate has been shown to improve BMD in the trabecular bone of the lumbar spine and hip (not distal radius) and may be used for asymptomatic patients with hyperparathyroidism who have a low BMD. It may also be combined with cinacalcet for the medical treatment of osteoporosis in patients with persistent hyperparathyroidism.

4. Denosumab—For patients with severe hypercalcemia due to parathyroid carcinoma, denosumab 120 mcg subcutaneously monthly may be effective. However, high-dose denosumab increases the risk of jaw osteonecrosis and serious infections.

5. Vitamin D and vitamin D analogs

A. PRIMARY HYPERPARATHYROIDISM—For patients with vitamin D deficiency, vitamin D replacement may be beneficial

to patients with hyperparathyroidism. Aggravation of hypercalcemia does not ordinarily occur. Serum PTH levels may fall with vitamin D replacement in doses of 800–2000 international units daily or more to achieve serum 25-OH vitamin D levels 30 ng/mL or more (50 nmol/L or more).

B. SECONDARY AND TERTIARY HYPERPARATHYROIDISM ASSOCIATED WITH AZOTEMIA—See Disorders of Mineral Metabolism, Kidney Disease.

6. Other measures—Estrogen replacement reduces hypercalcemia slightly in postmenopausal women with hyperparathyroidism. Similarly, oral raloxifene (60 mg/day) may be given to postmenopausal women with hyperparathyroidism; it reduces serum calcium an average of 0.4 mg/dL (0.1 mmol/L), while having an anti-estrogenic effect on breast tissue. Beta-blockers, such as propranolol, may also be useful for preventing the adverse cardiac effects of hypercalcemia. Parathyroid carcinoma metastases may be treated with radiofrequency ablation or arterial embolization.

C. Surgical Parathyroidectomy

Parathyroidectomy is recommended for patients with hyperparathyroidism who are symptomatic or who have nephrolithiasis or parathyroid bone disease. During pregnancy, parathyroidectomy is performed in the second trimester for women who are symptomatic or have a serum calcium above 11 mg/dL (2.75 mmol/L).

Some patients with seemingly asymptomatic hyperparathyroidism may be surgical candidates for other reasons such as (1) serum calcium 1 mg/dL (0.25 mmol/L) above the upper limit of normal, (2) urine calcium excretion greater than 400 mg/day (10 mmol/day), (3) estimated glomerular filtration rate less than 60 mL/min/1.73 m², (4) nephrolithiasis or nephrocalcinosis, (5) cortical bone density (wrist, hip, or distal radius) indicating osteoporosis (T score below -2.5) or previous fragility bone fracture, (6) relative youth (under age 50 years), (7) difficulty ensuring medical follow-up, or (8) pregnancy.

Surgery for patients with "asymptomatic" hyperparathyroidism may improve cortical BMD and confer modest benefits in social and emotional well-being and overall quality of life in comparison to similar patients being monitored without surgery. Cognitive function may benefit with improvements in nonverbal abstraction and memory.

Preoperative parathyroid imaging has been used in an attempt to allow unilateral minimally invasive neck surgery (see Imaging, above). The reported success rates vary considerably. Even in patients with concordant sestamibi and ultrasound scans, and an intraoperative PTH drop of more than 50%, hyperparathyroidism may persist postoperatively in up to 15% of patients.

Without preoperative localization studies, bilateral neck exploration is usually advisable for the following: (1) patients with a family history of hyperparathyroidism, (2) patients with a personal or family history of MEN, and (3) patients wanting an optimal chance of success with a single surgery. Parathyroid glands are often supernumerary (five or more) or ectopic (eg, intrathyroidal, carotid sheath, mediastinum). The optimal surgical management for patients with MEN type 1 is subtotal parathyroidectomy

that usually results in a cure, although recurrent hyperparathyroidism develops in 18% and the rate of postoperative hypoparathyroidism is high. About 30% of patients with successful parathyroid surgery continue to have an elevated serum PTH postoperatively, despite normal serum calcium levels; this is sometimes due to vitamin D deficiency.

Parathyroid hyperplasia is commonly seen with secondary or tertiary hyperparathyroidism associated with uremia. Cinacalcet is an alternative to surgery. When surgery is performed, a subtotal parathyroidectomy is optimal; three and one-half glands are usually removed, and a metal clip is left to mark the location of residual parathyroid tissue.

Parathyroid carcinoma surgery consists of en bloc resection of the tumor and ipsilateral thyroid lobe with care to avoid rupturing the tumor capsule. If the surgical margins are not clear of tumor, postoperative neck radiation therapy may be given. Local and distant metastases may be debulked or irradiated. Preoperative MRI scanning is required to delineate the tumor. Zoledronic acid or denosumab is given preoperatively. Severe hypercalcemia requires multiple medical measures, including hydration, furosemide, cinacalcet, zoledronic acid, or denosumab. Radiation therapy can be given for localized tumor. Osseous metastases must be distinguished from benign brown tumors caused by hyperparathyroidism; biopsy may be required. Chemotherapy has been ineffective for patients with distant metastases. Immunotherapy with anti-hPTH monoclonal antibodies is a treatment option.

Complications—Serum PTH levels fall below normal in 70% of patients within hours after successful surgery, commonly causing hypocalcemic paresthesias or even tetany. Hypocalcemia tends to occur the evening after surgery or on the next day. Frequent postoperative monitoring of serum calcium (or serum calcium plus albumin) is advisable beginning the evening after surgery. Once hypercalcemia has resolved, liquid or chewable calcium carbonate is given orally to reduce the likelihood of hypocalcemia. Symptomatic hypocalcemia is treated with larger doses of calcium; calcitriol (0.25–1 mcg daily orally) may be added, with the dosage depending on symptom severity. Magnesium salts are sometimes required postoperatively, since adequate magnesium is required for functional recovery of the remaining suppressed parathyroid glands.

In about 12% of patients having successful parathyroid surgery, PTH levels rise above normal (while serum calcium is normal or low) by 1 week postoperatively. This secondary hyperparathyroidism is probably due to “hungry bones” and is treated with calcium and vitamin D preparations. Such therapy is usually needed only for 3–6 months but is required long term by some patients.

Hyperthyroidism commonly occurs immediately following parathyroid surgery. It is caused by release of stored thyroid hormone during surgical manipulation of the thyroid. In symptomatic patients, short-term treatment with propranolol may be required for several days.

► Prognosis

Patients with symptomatic hyperparathyroidism usually experience worsening disease (eg, nephrolithiasis) unless they have treatment. Conversely, the majority of

completely asymptomatic patients with a serum calcium below 11.0 mg/dL (2.75 mmol/L) remain stable with follow-up. However, worsening hypercalcemia, hypercalcuria, and reductions in cortical BMD develop in about one-third of asymptomatic patients. Therefore, asymptomatic patients must be monitored carefully and treated with oral hydration and mobilization.

Surgical removal of apparently single sporadic parathyroid adenomas is successful in 94%. Patients with MEN 1 undergoing subtotal parathyroidectomy may experience long remissions, but hyperparathyroidism frequently recurs. Despite treatment for hyperparathyroidism, hypertension is usually not reversed and patients remain at increased risk for all-cause mortality, cardiovascular disease, renal calculi, and kidney dysfunction.

Spontaneous cure due to necrosis of the tumor is exceedingly rare. The bones, in spite of severe cyst formation, deformity, and fracture, will heal if hyperparathyroidism is successfully treated. The presence of pancreatitis increases the mortality rate. Acute pancreatitis usually resolves with correction of hypercalcemia, whereas subacute or chronic pancreatitis tends to persist. Kidney damage may progress even after removal of a parathyroid adenoma.

Parathyroid carcinoma is associated with 5- and 10-year survival rates of 78% and 49%, respectively. A better prognosis is associated with clear surgical margins and no detectable metastases postoperatively. Conversely, positive surgical margins or metastases predict a very poor 5-year survival. The prognosis is also poorer for nonfunctioning parathyroid carcinoma and those tumors that carry a *CDC73* mutation, loss of fibromin, or loss of CaSR expression. Repeat surgical debulking procedures may improve survival. Aggressive medical management can also prolong life. Metastases are relatively radiation-resistant, but additional therapies such as radiofrequency ablation or arterial embolization may be palliative.

► When to Refer

Refer to parathyroid surgeon for parathyroidectomy.

► When to Admit

Patients with severe hypercalcemia for intravenous hydration.

Davis C et al. Hyperparathyroidism in pregnancy. BMJ Case Rep. 2020;13:e232653. [PMID: 32066577]

Leere JS et al. Denosumab and cinacalcet for primary hyperparathyroidism (DENOCINA): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Diabetes Endocrinol. 2020;8:407. [PMID: 32333877]

Rodrigo JP et al. Parathyroid cancer: an update. Cancer Treat Rev. 2020;86:102012. [PMID: 32247225]

Zhu CY et al. Diagnosis and management of primary hyperparathyroidism. JAMA. 2020;323:1186. [PMID: 32031566]

METABOLIC BONE DISEASE

BMD is typically expressed in g/cm², for which there are different normal ranges for each bone and for each type of DXA-measuring machine. The “Z score” expresses an individual’s BMD as the number of standard deviations from

age-matched, race-matched, and sex-matched means. The “T score” reports BMD as the number of standard deviations from young sex-matched means. Patients with a low T score are said to have “osteopenia” or “osteoporosis,” although osteomalacia is also frequently present. Any BMD classification is somewhat arbitrary and there is no BMD fracture threshold; instead, fracture risk increases about twofold for each standard deviation drop in BMD. The World Health Organization has established criteria for defining osteopenia and osteoporosis based on the T score: T score greater than or equal to -1.0 , normal; T score -1.0 to -2.5 , osteopenia (“low bone density”); T score less than -2.5 , osteoporosis; T score less than -2.5 with a fracture, severe osteoporosis.

Fracture Risk Assessment Tool (FRAX) helps predict an individual’s 10-year risk of hip or other major osteoporotic fracture. FRAX is particularly useful for treatment decisions in patients with osteopenia and takes into consideration age, sex, BMD, and other risk factors. The National Osteoporosis Foundation recommends treatment for individuals with osteopenia (T score between -1.0 and -2.5) who have a computed 10-year hip fracture risk of at least 3% or a 10-year risk of any major fracture of at least 20%. However, the FRAX model has limitations, since it only considers femoral neck BMD and not vertebral BMD. Also, FRAX does not consider the dose of exposure to corticosteroids, race, alcohol, smoking, or an individual’s proclivity to falls; treatment decisions must always be individualized. FRAX is available at <https://www.sheffield.ac.uk/FRAX/tool.aspx/>.

Black DM et al. Treatment-related changes in bone mineral density as a surrogate biomarker for fracture risk reduction: meta-regression analyses of individual patient data from multiple randomised controlled trials. Lancet Diabetes Endocrinol. 2020;8:672. [PMID: 32707115]

DeSapri KT et al. To scan or not to scan? DXA in postmenopausal women. Cleve Clin J Med. 2020;87:205. [PMID: 32238375]

OSTEOPENIA



ESSENTIALS OF DIAGNOSIS

- ▶ Patients are typically asymptomatic.
- ▶ Bone density below that for young normal adults but less severe than osteoporosis.
- ▶ Diagnosis is by DXA.
- ▶ Fracture risk determined with FRAX tool.

General Considerations

Osteopenia is less severe than osteoporosis, with T scores between -1.0 and -2.4 (see above). There is no absolute fracture threshold for BMD, and most patients with bone fractures are found to have osteopenia rather than osteoporosis. Patients who are identified as osteopenic require an evaluation for causes of osteoporosis or osteomalacia and monitoring for worsening BMD.

Clinical Findings

A. Symptoms and Signs

Patients with osteopenia are typically asymptomatic. However, bone pain can be present, particularly with osteomalacia. Osteopenia predisposes to low-impact and pathological fractures of vertebrae, hips, wrists, metatarsals, and ribs.

B. Laboratory Findings

Patients with moderate to severe osteopenia (T scores between -1.5 and -1.4) require an evaluation for underlying causes of osteoporosis and osteomalacia. Testing should include a serum BUN, creatinine, albumin, calcium, phosphate, alkaline phosphatase, and 25-OH vitamin D; a complete blood count is also recommended. A serum PTH is obtained if the serum calcium is abnormal.

C. DXA Bone Densitometry and FRAX

Osteopenia is diagnosed by DXA bone densitometry with T scores of -1.0 to -2.4 . The frequency of surveillance DXA testing for postmenopausal women and elderly men should be based on the T scores: obtain DXA testing every 5 years for T scores -1.0 to -1.5 , every 3–5 years for T scores -1.5 to -2.0 , and every 1–2 years for T scores below -2.0 . Patients requiring high-dose long-term prednisone therapy should have DXA surveillance every 1–2 years. FRAX score (see above) should be determined with each DXA BMD determination.

Prevention & Treatment

Patients with osteopenia require adequate vitamin D intake to achieve serum 25-OH vitamin D levels above 30 ng/mL (75 nmol/L). Calcium supplementation is not usually required, except for patients with unusually low dietary calcium intake. Lifestyle modifications may be required, including smoking cessation, alcohol moderation, strength training and weight-bearing exercise. Balance exercises such as tai chi may help prevent falls. Other fall prevention measures include reduction of tranquilizer and alcohol consumption, visual or walking aids when warranted, removal of home tripping hazards, and adequate night lighting.

Pharmacologic therapy is not usually required for patients with osteopenia. However, pharmacologic intervention treatments (see osteoporosis) may be required for patients who require long-term high-dose prednisone, for patients with fragility fractures, and for those whose FRAX score indicates a 10-year risk for fracture above 20% or hip fracture risk above 3%.

Iqbal SM et al. Role of bisphosphonate therapy in patients with osteopenia: a systemic review. Cureus. 2019;11:e4146. [PMID: 31058029]

Zhang Y et al. Tai chi for treating osteopenia and primary osteoporosis: a meta-analysis and trial sequential analysis. Clin Interv Aging. 2019;14:91. [PMID: 30655662]

OSTEOPOROSIS



ESSENTIALS OF DIAGNOSIS

- ▶ Fracture propensity of spine, hip, pelvis, and wrist.
- ▶ Asymptomatic until a fracture has occurred.
- ▶ Serum PTH, calcium, phosphorus, and alkaline phosphatase usually normal.
- ▶ Serum 25-hydroxyvitamin D levels often low as a comorbid condition.

General Considerations

Osteoporosis is a skeletal disorder characterized by a loss of bone matrix (osteoid) that reduces bone integrity and bone strength, predisposing to an increased risk of fragility and fracture. In the United States, osteoporosis causes over 1.5 million fractures annually. White women age 50 years and older (who do not receive estrogen replacement) have a 46% risk of sustaining an osteoporotic fracture during the remainder of their lives. Vertebral fractures are the most common fracture; they are usually diagnosed incidentally on radiographs or CT scanning.

Largely due to a reduction in smoking, the age-adjusted risk for hip fracture has declined in the United States in recent years. However, the risk for fragility fractures remains high and varies with ethnicity, sex, and age. The lifetime risk of hip fracture is 12.1% in White women and 4.6% in White men. The risks are lower in Hispanic women and men and lower yet in Chinese women and men (with similar gender differences). Blacks also have a lower risk for fracture due to higher BMD and hip morphology that is less fracture-prone. There is much less ethnic variability for vertebral fractures. The prevalence of vertebral fractures in women older than 65 years is 70% for White women, 68% for Japanese women, 55% for Mexican women, and 50% in Black women.

Osteoporosis can be caused by a variety of factors (Table 26–10). The most common causes include aging, sex hormone deficiency, alcohol use disorder, cigarette smoking, long-term proton pump inhibitor therapy, and high-dose corticosteroid administration. Women who chronically consume cola beverages are at increased risk for osteoporosis of the hip. Hypogonadal men frequently develop osteoporosis. Anti-androgen therapy for prostate cancer can cause osteoporosis, and such men should be monitored with bone densitometry.

Clinical Findings

A. Symptoms and Signs

Osteoporosis is usually asymptomatic until fractures occur, which may present as backache of varying degrees of severity or as a spontaneous fracture, collapse of a vertebra, or spinal kyphosis. Loss of height is common. Vertebral fractures and hip fractures are associated with increased mortality, pain, reduced independence, and diminished quality

Table 26–10. Causes of osteoporosis.¹

Aging	Medications (long-term)
Alcohol use disorder (alcoholism)	Aromatase inhibitors
Cigarette smoking	Corticosteroids
Cola consumption in women (hip)	GnRH inhibitors
Ethnicity: White	Heparin
Female sex	Pioglitazone
Genetic disorders	Proton pump inhibitors
Aromatase deficiency	Selective serotonin reuptake inhibitors (elderly)
Collagen disorders	SGLT2 inhibitors
Ehlers-Danlos syndrome	Vitamin A excess, vitamin D excess
Homocystinuria	Underweight (BMI < 18.5)
Hypophosphatasia	Miscellaneous conditions
Idiopathic juvenile and adult osteoporosis	Anorexia nervosa
Marfan syndrome	Celiac disease
Osteogenesis imperfecta	Copper deficiency
Hormone deficiency	Cystic fibrosis
Estradiol (women)	Diabetes mellitus (uncontrolled)
Testosterone (men)	HIV infection
Hormone excess	Hyponatremia (chronic)
Cushing syndrome	Inflammatory bowel disease
Hyperparathyroidism	Liver disease (chronic)
Thyrotoxicosis	Mastocytosis (systemic)
Low physical activity and immobilization	Primary biliary cholangitis
Malignancy, especially plasma cell myeloma	Protein-calorie malnutrition
	Rheumatoid arthritis
	Thalassemia major
	Vitamin C deficiency

¹See Table 26–11 for causes of osteomalacia.

of life. Once osteoporosis is identified, a directed history and physical examination must be performed to determine its cause (Table 26–10).

B. Laboratory Findings

DXA bone densitometry is required to diagnose osteoporosis (T score less than –2.5) (see above). **Laboratory testing** is required to screen for secondary causes of osteoporosis or concomitant osteomalacia. For patients with a low bone densitometry, obtain serum determinations for BUN, creatinine, albumin, serum calcium, phosphate, alkaline phosphatase, and 25-hydroxyvitamin D (25HD, 25-hydroxycalciferol). A serum PTH is obtained if the serum calcium is abnormal. A low serum alkaline phosphatase (below 40 units/L in adults) may indicate hypophosphatasia. A complete blood count is obtained and is usually normal; for patients with anemia, screen for plasma cell myeloma with a serum protein electrophoresis and screen for intestinal malabsorption, where indicated. Serum 25HD levels below 20 ng/mL (50 nmol/L) are considered frank vitamin D deficiency. Lesser degrees of vitamin D insufficiency (serum 25HD levels in the range of 20–30 ng/mL [50–75 nmol/L]) may also slightly increase the risk for hip fracture. Test for thyrotoxicosis and hypogonadism, if clinically warranted. Celiac disease may be screened for with serum tissue transglutaminase antibody determinations.

Differential Diagnosis

Osteopenia and fractures can be caused by osteomalacia and bone marrow neoplasia such as plasma cell myeloma or metastatic bone disease. Hypophosphatasia also causes diminished bone density. These conditions coexist in many patients and cannot be distinguished with bone densitometry.

Prevention & Treatment

A. Nonpharmacologic Measures

For prevention and treatment of osteoporosis, the diet should be adequate in protein, total calories, calcium, and vitamin D. Pharmacologic corticosteroid (oral, parenteral, or inhaled) should be reduced or discontinued if possible. Cigarette smoking cessation is essential. Excessive alcohol intake must be avoided. Exercise is strongly recommended to increase both bone density and strength, thereby reducing the risk of fractures due to frailty falls. Walking increases the bone density at both the spine and hip. Resistance exercise increases spine density. The patient must choose an enjoyable exercise regimen to facilitate long-term compliance. Other fall prevention measures include adequate home lighting, handrails on stairs, handholds in bathrooms, and physical therapy training in fall prevention and balance exercises. Patients who have weakness or balance problems must use a cane or a walker; rolling walkers should have a brake mechanism. Medications that cause orthostasis, dizziness, or confusion should be avoided.

B. Pharmacologic Measures

Generally, treatment is indicated for patients with osteoporosis diagnosed by DXA, particularly those who have had recent fragility fractures, women with previous fragility fractures of the hip or vertebra, or a DXA T score between -2.5 and -1.0 with FRAX-determined 10-year hip fracture risk greater than 3% or major osteoporotic fracture risk greater than 20% (see above). Osteoporosis treatment does reduce fracture risk but does not improve overall mortality.

1. Vitamin D and calcium—Deficiency of vitamin D or calcium causes osteomalacia, rather than osteoporosis, but they often coexist and cannot be distinguished by DXA bone densitometry; it is crucial to ensure sufficient vitamin D and calcium intake. Recommended daily vitamin D intake of 600–800 international units/day is difficult to achieve by diet (unless high in fish) and sun exposure, particularly during winter months and for patients with intestinal malabsorption or during prolonged hospitalization or nursing home care. Oral vitamin D₃ (cholecalciferol) is given either as a universal supplement of 800–2000 international units/day or in doses titrated to achieve 25-hydroxyvitamin D (25-OHD) serum levels greater than or equal to 20 ng/mL (50 nmol/L) for most of the population. However, the 25-OHD serum levels should be maintained at 30 ng/mL (75 nmol/L) or higher for those “at risk”: pregnant women, older adults, and those with osteoporosis or fragility fractures. Doses of vitamin D₃ above 4000 international units daily in adults are generally not advised (except in patients with intestinal malabsorption), since

gastrointestinal side effects or hypercalcemia may occur. Vitamin D should not be taken with topical calcipotriene to avoid hypercalcemia. There are early observational data that imply an increased all-cause mortality at 25-OHD serum levels that are either excessively low or high, so the optimal therapeutic range for 25-OHD serum levels appears to be about 30–50 ng/mL (75–125 nmol/L).

A total elemental calcium intake at least 1000 mg/day is recommended for all adults and 1200 mg/day for postmenopausal women and men older than 70 years. Many individuals do not consume this amount of calcium, but a large prospective study of osteopenic postmenopausal women showed no improvement in BMD with high calcium consumption. Also, most cohort studies have shown no association between dietary calcium intake and fracture risk. Other studies have reported that associated calcium supplementation (1 g/day or more) showed no reduced risk for hip or forearm fractures and a mere 14% reduction in vertebral fractures. Therefore, normal and osteopenic individuals do not require calcium supplementation. Calcium supplements are reserved for patients with intestinal malabsorption or calcium-deficient diets that do not include dairy products, dark leafy greens, sardines, tofu, or fortified foods. Calcium citrate does not require acid for absorption and is preferred for patients receiving acid blockers. Calcium carbonate should be taken with food to enhance calcium absorption. Calcium supplements are usually taken along with vitamin D₃, and many commercial supplements contain the combination.

Some reports have indicated that calcium supplements increase the risk of myocardial infarction. However, the Women's Health Initiative found that 7 years of vitamin D and calcium supplementation did not increase cardiovascular disease but did increase the risk of nephrolithiasis by 13%. Taking calcium supplements with meals can reduce the risk of nephrolithiasis. Although calcium supplements are usually tolerated, some patients experience intestinal bloating and constipation.

2. Sex hormones—Sex hormone replacement can prevent osteoporosis in hypogonadal women and men but is not an effective therapy for established osteoporosis. Low-dose transdermal systemic estrogen prevents osteoporosis in women with hypogonadism, including young patients with anorexia nervosa (see Hormone Replacement Therapy). Testosterone replacement or low-dose transdermal estradiol therapy prevents osteoporosis in men with severe testosterone deficiency (see Male Hypogonadism).

3. Bisphosphonates—Bisphosphonate therapy is indicated for patients with osteoporosis in the spine, total hip, or femoral neck or for patients with a pathologic spine fracture or a low-impact hip fracture. Bisphosphonates include intravenous zoledronic acid or pamidronate and oral alendronate, risedronate, or ibandronate. Ibandronate reduces vertebral fracture risk but not nonvertebral fracture risk. Bisphosphonates all work similarly, inhibiting osteoclast-induced bone resorption. They increase bone density significantly and all reduce the incidence of vertebral fractures; all but ibandronate have been demonstrated to also reduce the risk of nonvertebral fractures. Bisphosphonates have

also been effective in preventing corticosteroid-induced osteoporosis. Another possible advantage is a reduction in adverse cardiovascular events. Oral alendronate was associated with a 33% reduction in cardiovascular events in a Danish cohort. To ensure intestinal absorption, oral bisphosphonates must be taken in the morning with at least 8 oz of plain water at least 40 minutes before consumption of anything else. The patient must remain upright after taking bisphosphonates to reduce the risk of esophagitis. No dosage adjustments are required for patients with creatinine clearances above 35 mL/min. Bisphosphonates are excreted in urine and serum phosphate levels should be monitored in patients with kidney disease; bisphosphonates are relatively contraindicated in patients with CrCl below 35 mL/min. Bone density falls in 18% of patients during their first year of treatment with bisphosphonates, but 80% of such patients gain bone density with continued bisphosphonate treatment. The half-life of bisphosphonates in bone is about 10 years. Therefore, after 3 years, a DXA bone densitometry may be obtained. If the patient's T score has risen above -2.5 and the patient has a relatively low fracture risk, the patient may have a bisphosphonate "drug holiday" for 3–5 years. However, for patients with continued osteoporosis and a high fracture risk, the bisphosphonate may be continued another 2 years. The usual treatment course with bisphosphonates is 3–5 years due to the increasing risk of atypical femoral fractures after that time.

Alendronate is administered orally once weekly as either a 70-mg standard tablet (Fosamax) or a 70-mg effervescent pH-buffered tablet (Binosto). The effervescent tablet must be dissolved in 4 oz plain water over at least 5 minutes and stirred 10 seconds before drinking; it is easier to swallow for some patients and may reduce esophageal injury, but there have been no studies comparing it to standard alendronate tablets. **Risedronate** (Actonel) may be given once monthly as a 150-mg tablet. Risedronate is favored for women of childbearing age, since it has a shorter half-life and less bone retention than other bisphosphonates. Both medications reduce the risk of vertebral and nonvertebral fractures, but alendronate appears to be superior to risedronate in preventing nonvertebral fractures. **Ibandronate sodium** (Boniva) is taken once monthly in a dose of 150 mg orally. It reduces the risk of vertebral fractures but not nonvertebral fractures; its effectiveness has not been directly compared with other bisphosphonates.

For patients who cannot take oral bisphosphonates, intravenous bisphosphonates are available. They should not be given to patients with a creatinine clearance below 35 mL/min. Patients should receive at least 15 minutes of intravenous hydration prior to infusions. **Zoledronic acid** (Reclast) is a third-generation bisphosphonate and a potent osteoclast inhibitor. The dose is 5 mg intravenously over at least 15–30 minutes every 12 months. In a study of postmenopausal women with osteoporosis, once yearly intravenous zoledronic acid reduced the 3-year incidence of hip fractures by 41% (from 2.5% to 1.4%) and clinical vertebral fractures by 77% (from 2.6% to 0.5%). **Pamidronate** (Aredia), another bisphosphonate, is given in doses of 30–60 mg by slow intravenous infusion in normal saline solution every 3–6 months.

SIDE EFFECTS OF BISPHOSPHONATES—Oral bisphosphonates can cause nausea, chest pain, and hoarseness. Erosive esophagus can occur, particularly in patients with hiatal hernia and gastroesophageal reflux. Although no increased risk of esophageal cancer has been conclusively demonstrated, the FDA recommends that oral bisphosphonates not be used by patients with Barrett esophagus.

Intravenous bisphosphonate therapy can cause side effects that are collectively known as the acute-phase response. Such a response occurs in 42% of patients after the first infusion of zoledronic acid and usually starts within the first few days following the infusion; these adverse side effects include fever, chills, or flushing (20%); musculoskeletal pain (20%); nausea, vomiting, or diarrhea (8%); nonspecific symptoms, such as fatigue, dyspnea, edema, headache, or dizziness (22%); and ocular inflammation (0.6%). Intravenous zoledronic acid has caused seizures that may be idiosyncratic or due to hypocalcemia. The acute-phase response tends to diminish with time. Symptoms are transient, lasting several days and usually resolving spontaneously but typically recurring with subsequent doses. Symptoms may be treated with acetaminophen or NSAIDs. Loratadine may reduce musculoskeletal pain. For patients experiencing a severe acute-phase response with zoledronic acid, intravenous pamidronate can be substituted for subsequent treatments. The acute-phase response after pamidronate is usually less severe than that of zoledronic acid. In addition, patients who experience an especially severe acute-phase response can be given prophylactic corticosteroids and ondansetron prior to subsequent bisphosphonate infusions.

Osteonecrosis of the jaw is a rare complication of bisphosphonate therapy. A painful, necrotic, nonhealing lesion of the jaw occurs, particularly after tooth extraction. It occurs twice as frequently in the mandible compared to the maxilla. The risk is increased with older age, in women, and in patients concomitantly receiving chemotherapy or corticosteroid therapy. About 95% of jaw osteonecrosis cases have occurred with intravenous high-dose therapy with zoledronic acid or pamidronate for patients with osteolytic metastases. Only about 5% of cases have occurred in patients receiving oral bisphosphonates or once-yearly bisphosphonate infusions for osteoporosis. The incidence of osteonecrosis is estimated to be about 1:100,000 patients treated for osteoporosis with oral bisphosphonates and 1:100 patients being treated for cancer with intravenous bisphosphonates. The risk for osteonecrosis of the jaw with dental surgery can be approximated preoperatively with a serum level of C-telopeptide, a fragment of collagen released during bone remodeling. Bisphosphonates reduce C-telopeptide levels. Serum C-telopeptide levels greater than or equal to 150 pg/mL are associated with a minimal risk of osteonecrosis, whereas C-telopeptide levels of 100–149 pg/mL are associated with a moderate risk, and C-telopeptide levels less than 100 pg/mL are associated with a high risk for osteonecrosis. Patients receiving bisphosphonates must receive regular dental care and try to avoid dental extraction. Ideally, elective dental surgery should be completed before starting bisphosphonates. If dental surgery is required, bisphosphonate therapy is

ordinarily stopped 3 months before the surgery and may be resumed about 1 month afterward if the bone has healed.

Atypical low-impact “chalkstick” fractures of the femoral shaft are an uncommon complication of bisphosphonate therapy. Asian women, however, experience a relative risk of atypical femur fracture that is 4.8 times higher than White women. In more than 52,000 postmenopausal women taking bisphosphonates for 5 years or longer, a subtrochanteric fracture occurred in 0.22% during the subsequent 2 years; 27% of such fractures were bilateral. About 70% of affected patients have had prodromal thigh pain prior to the fracture. The risk for atypical femoral fractures is particularly increased among Asian women and among patients taking high-dose corticosteroids and those receiving bisphosphonate treatment for more than 5 years. Teriparatide (a PTH analog) may be helpful to promote healing of such fractures. Despite this potential complication, the benefits of bisphosphonates outweigh the risks, particularly in non-Asian women. In a large cohort analysis, for every 10,000 women taking bisphosphonates for 3 years, 149 hip fractures were prevented and 2 atypical femur fractures occurred in White women, while 91 hip fractures were prevented and 8 atypical femur fractures occurred in Asian women.

In patients taking bisphosphonates, hypercalcemia is seen in 20% and serum PTH levels increase above normal in 10%, mimicking primary hyperparathyroidism. Hypocalcemia occurs frequently, resulting in secondary hyperparathyroidism; such patients may be treated with oral calcium salt supplements (500–1000 mg/day) and with oral vitamin D₃ (starting at 1000 units/day).

4. Denosumab—Denosumab (Prolia) is a monoclonal antibody that inhibits the proliferation and maturation of preosteoclasts into mature osteoclast bone-resorbing cells. It is indicated for treatment of osteoporosis, major fragility fractures, or osteopenia with a high FRAX score in both men and women. It is also used for patients with high fracture risk who are receiving sex hormone suppression therapy for breast cancer or prostate cancer. Treatment reduces vertebral fractures by 68% and reduces hip fractures by 40%. Denosumab is administered in doses of 60 mg subcutaneously every 6 months. Unlike bisphosphonates, denosumab can be given to patients with severe kidney disease. It has been relatively well tolerated, with an 8% incidence of flu-like symptoms. It can decrease serum calcium and should not be administered to patients with hypocalcemia. Other side effects include hypercholesterolemia, eczema and dermatitis, and pancreatitis. Denosumab may slightly increase the risk of serious infections (particularly ear, nose, throat, and gastrointestinal), so it is not recommended for patients receiving immunosuppressants or high-dose corticosteroid therapy. *In premenopausal women, denosumab should be used with great caution and with birth control, since denosumab has caused fetal teratogenicity in animal studies.* With prolonged use, denosumab predisposes to atypical femoral fractures and osteonecrosis of the jaw and is additive to bisphosphonates in that regard.

Compared to oral bisphosphonates, denosumab appears to be slightly superior at improving BMD of the spine, total femur, and femoral neck and at reducing fracture risk after 2 years of therapy. Compared to intravenous zoledronic

acid, denosumab has been somewhat superior at increasing BMD at the total femur and femoral neck, but the two have similar efficacy at improving spine BMD.

The effects of denosumab on bone wane quickly after 6 months, and patients can experience a dramatic increased risk of multiple vertebral fractures within 1–2 years following discontinuation of denosumab. Therefore, denosumab must be given on-schedule without drug holidays. Denosumab should not be discontinued without substituting another antiresorptive agent (bisphosphonate, estradiol, or selective estrogen receptor modulator [SERM]) or other therapy.

5. PTH and PTHrP analogs—Teriparatide (Forteo) and abaloparatide (Tymlos) are analogs of PTH and PTHrP, respectively. They are indicated only for patients with osteoporosis who are at very high fracture risk, particularly those who have sustained severe or multiple vertebral fractures. These analogs are anabolic agents that stimulate the production of new collagenous bone matrix, particularly in vertebral trabecular bone that must be mineralized. Patients receiving teriparatide or abaloparatide must have sufficient intake of vitamin D and calcium. When given in a sequence with an antiresorptive agent, the preferred sequence is to first give a course of PTH/PTHrP analog therapy followed by a bisphosphonate or denosumab.

The teriparatide dose is 20 mg or 40 mg daily, and the abaloparatide dose is 80 mg daily; both are given subcutaneously daily for up to 2 years. These drugs dramatically improve bone density in most bones except the distal radius. They may also be used to promote healing of atypical femoral chalkstick fractures associated with bisphosphonate therapy. The recommended dose should not be exceeded, since both drugs have caused osteosarcoma in rats when administered long-term in very high doses. Due to the potential risk for osteosarcoma, patients are excluded from receiving teriparatide or abaloparatide if they have an increased risk of osteosarcoma due to the following: Paget disease of bone, unexplained elevations in serum alkaline phosphatase, prior radiation therapy to bones, open epiphyses, or a past history of osteosarcoma or chondrosarcoma. Side effects may include injection site reactions, orthostatic hypotension, arthralgia, muscle cramps, depression, or pneumonia. Hypercalcemia can occur and manifest as nausea, constipation, asthenia, or muscle weakness. These drugs are approved for only a 2-year course of treatment.

Teriparatide and abaloparatide should not be used for patients with hypercalcemia. Similarly, they should be used with caution in patients if they are also taking corticosteroids and thiazide diuretics along with oral calcium supplementation because hypercalcemia may develop.

Following a 2-year course of teriparatide or abaloparatide, bisphosphonates should be given to retain the improved bone density. Alternatively, for very severe osteoporosis, these drugs may be administered along with denosumab; combined treatment for 2 years is more effective than any other single therapy, but adverse effects of fatigue, joint pain, and nausea are very common.

6. SERMs—SERMs can prevent osteoporosis but are not effective therapy for established osteoporosis. **Raloxifene** 60 mg/day orally may be taken by postmenopausal women

in place of estrogen for prevention of osteoporosis. Bone density increases about 1% over 2 years in postmenopausal women versus 2% increases with estrogen replacement. It reduces the risk of vertebral fractures by about 40% but does not appear to reduce the risk of nonvertebral fractures. It has no direct effect on coronary plaque. Unlike estrogen, raloxifene does not reduce hot flushes; in fact, it often intensifies them. It does not relieve vaginal dryness. Unlike estrogen, however, raloxifene does not cause endometrial hyperplasia, uterine bleeding, or cancer, nor does it cause breast soreness. The risk of breast cancer is reduced 76% in women taking raloxifene for 3 years. Since it is a potential teratogen, it is relatively contraindicated in women capable of pregnancy. Raloxifene increases the risk for thromboembolism and should not be used by women with such a history. Leg cramps can also occur. **Tamoxifen** is commonly administered to women for up to 5 years after resection of breast cancer that is estrogen receptor-positive. Tamoxifen has opposite effects on bone density in premenopausal versus postmenopausal women. In premenopausal women, tamoxifen causes a *loss* of vertebral bone mineral density of -1.44% yearly, whereas in postmenopausal women, tamoxifen causes an *increase* in vertebral bone mineral density of +1.17% yearly. **Bazedoxifene** is available as a fixed-dose combination of conjugated estrogens with a SERM (bazedoxifene) (0.45 mg/20 mg [Duavee]). It is FDA approved for the prevention of osteoporosis in postmenopausal women with an intact uterus. However, unlike raloxifene, it has not been shown to reduce the risk of breast cancer. Women taking this combination medication long-term experience an increased risk of thromboembolic events.

7. Calcitonin—Nasal salmon calcitonin is used primarily for its analgesic effect for the pain of acute osteoporotic vertebral compression fractures. It is ineffective for chronic pain. Its analgesic effect may be seen within 2–4 weeks. If it appears to be effective for analgesia, it is continued for up to 3 months. The usual dose of nasal spray of calcitonin-salmon (Miacalcin) contains one puff (0.09 mL, 200 international units) once daily, alternating nostrils. Nasal symptoms such as rhinitis and epistaxis occur commonly; other less common adverse reactions include flu-like symptoms, allergy, arthralgias, back pain, headache, and hypocalcemia. Salmon calcitonin is available in an injectable form that can be used when the nasal formulation is not tolerated due to local reactions; it is used for up to 3 months for vertebral fracture pain in doses of 100 international units subcutaneously or intramuscularly every 1–2 days. Calcitonin's anti-osteoporosis effect is modest, so it is only used to treat osteoporosis in patients who cannot tolerate other therapies. Also, while long-term calcitonin therapy reduces the risk of breast cancer, it appears to increase the overall risk of malignancy by about 1.1%, particularly hepatic cancer. It has been withdrawn from the market in Canada and Europe.

8. Romosozumab—Romosozumab (Evenity) is an injectable monoclonal antibody that inhibits sclerostin, increasing new bone formation and decreasing bone resorption. In one large cohort of women with osteoporosis and fragility fractures, those treated with romosozumab for

12 months followed by alendronate for 12 months had a 48% lower risk of new vertebral fractures and a 38% lower risk of hip fracture compared to women receiving alendronate alone. The dose is 210 mg subcutaneously monthly for up to 12 months. It is reserved for patients with very severe osteoporosis, such as those with multiple vertebral fractures. It should only be given to patients with a low risk of coronary disease or stroke, since it may slightly increase the risk of adverse cardiovascular events.

► Prognosis

Osteoporosis should ideally be prevented, since it can be only partially reversed. Measures noted above are reasonably effective in preventing and treating osteoporosis and reducing fracture risk.

Black DM et al. Atypical femur fracture risk versus fragility fracture prevention with bisphosphonates. *N Engl J Med.* 2020;383:743. [PMID: 32813950]

Camacho PM et al. American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines for the diagnosis and treatment of postmenopausal osteoporosis—2020 update. *Endocr Pract.* 2020;26:1. [PMID: 32427503]

Eastell R et al. Pharmacological management of osteoporosis in postmenopausal women: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2019;104:1595. [PMID: 30907953]

Grossman DC et al. Vitamin D, calcium, or combined supplementation for the primary prevention of fractures in community-dwelling adults: US Preventive Services Task Force Recommendation Statement. *JAMA.* 2018;319:1592. [PMID: 29677309]

Rodriguez AJ et al. Oral bisphosphonate use reduces cardiovascular events in a cohort of Danish patients referred for bone mineral density. *J Clin Endocrinol Metab.* 2020;105:dcaa481. [PMID: 32717068]

Shoback D et al. Pharmacological management of osteoporosis in postmenopausal women: an Endocrine Society guideline update. *J Clin Endocrinol Metab.* 2020;105:587. [PMID: 32068863]

RICKETS & OSTEOMALACIA

ESSENTIALS OF DIAGNOSIS

- ▶ Low bone density from defective mineralization.
- ▶ Caused by deficiency in calcium, phosphorus, or low alkaline phosphatase.
- ▶ **Rickets:** defective bone mineralization in childhood or adolescence before epiphyseal fusion.
- ▶ **Osteomalacia:** defective bone mineralization in adults with fused epiphyses.
- ▶ Painful proximal muscle weakness (especially pelvic girdle); bone pain.
- ▶ Low serum 25-hydroxy-vitamin D (25-OHD), hypocalcemia, hypocalciuria, hypophosphatemia, secondary hyperparathyroidism.
- ▶ Classic radiologic features may be present.

► General Considerations

Defective mineralization of the growing skeleton in childhood causes permanent bone deformities (rickets). Defective skeletal mineralization in adults is known as osteomalacia. It is caused by inadequate calcium or phosphate mineralization of bone osteoid.

► Etiology

Causes of osteomalacia are listed in Table 26–11.

A. Vitamin D Deficiency

Vitamin D deficiency is the most common cause of osteomalacia; its incidence is increasing throughout the world as a result of diminished exposure to sunlight caused by urbanization with use of automobile and public transportation, living at high latitudes, winter season, institutionalization, sunscreen use, or very modest dressing. About 36% of adults in the United States are deficient in vitamin D.

Other risk factors for vitamin D deficiency include the following: pregnant women, age over 65 years, obesity, dark skin, malnutrition, and intestinal malabsorption. Orlistat causes fat and vitamin D malabsorption. Cholestryamine binds bile acids necessary for vitamin D absorption. Patients with severe nephrotic syndrome lose large amounts of vitamin D-binding protein in the urine.

Table 26–11. Causes of osteomalacia.¹

Vitamin disorders
Insufficient sunlight exposure
Kidney: chronic kidney disease, nephrotic syndrome, kidney transplantation
Liver disease
Nutritional deficiency of vitamin D
Malabsorption: aging, excess wheat bran, bariatric surgery, pancreatic enzyme deficiency, orlistat
Vitamin D-dependent rickets types I and II
Phenytoin, carbamazepine, valproate, or barbiturate therapy (long-term)
Dietary calcium deficiency
Phosphate deficiency
Adefovir therapy
Fanconi syndrome, renal tubular acidosis, and alcoholism
Intestinal malabsorption
Nutritional deficiency of phosphorus
Phosphate-binding antacid therapy
Renal loss
Tumoral hypophosphatemic osteomalacia
X-linked hypophosphatemic rickets
Other disorders, including paraproteinemias, glycogen storage diseases, neurofibromatosis, Wilson disease
Inhibitors of mineralization
Aluminum
Bisphosphonates
Disorders of bone matrix
Axial osteomalacia
Hypophosphatasia
Fibrogenesis imperfecta

¹See Table 26–10 for causes of osteoporosis.

Anticonvulsants (eg, phenytoin, carbamazepine, valproate, phenobarbital) inhibit the hepatic production of 25-OHD and sometimes cause osteomalacia. Phenytoin can also directly inhibit bone mineralization.

Vitamin D-dependent rickets type I is caused by a rare autosomal recessive disorder with a defect in the renal enzyme 1-alpha-hydroxylase leading to defective synthesis of 1,25(OH)₂D.

Vitamin D-dependent rickets type II (hereditary 1,25[OH]₂D-resistant rickets) is caused by a genetic defect in the 1,25(OH)₂D receptor.

B. Calcium Deficiency

The total daily consumption of calcium should be at least 1000 mg daily. Patients who have deficient calcium intake develop rickets (childhood) or osteomalacia (adulthood) despite sufficient vitamin D. A nutritional deficiency of calcium can occur in any severely malnourished patient. Some degree of calcium deficiency is common in older adults, since intestinal calcium absorption declines with age. Ingestion of excessive wheat bran also causes calcium malabsorption.

C. Phosphate Deficiency

Osteomalacia develops in patients with hypophosphatemia due to lack of sufficient phosphate to mineralize bone osteoid. Such patients typically have musculoskeletal pain, muscle weakness, and are prone to fractures.

1. Genetic disorders—Fibroblast growth factor-23 (FGF23) is a phosphaturic factor (phosphatonin) that is secreted by bone osteoblasts in response to elevated serum phosphate levels. Various genetic mutations can result in high serum FGF23 levels, causing hypophosphatemia and bone mineral depletion.

2. Tumor-induced osteomalacia—This is a rare paraneoplastic syndrome that can be caused by a variety of mesenchymal tumors (87% benign) secrete FGF23 and cause marked hypophosphatemia due to renal phosphate wasting. Such tumors are usually phosphaturic mesenchymal tumors (70%); other tumors include hemangiopericytomas, osteosarcomas, and giant cell tumors. The condition is characterized by hypophosphatemia, excessive phosphaturia, reduced or normal serum 1,25(OH)₂D concentrations, and osteomalacia. Serum levels of FGF23 are elevated. Such tumors are often small and difficult to find, frequently lying in the sinuses or extremities.

3. Other causes of hypophosphatemia—Osteomalacia from hypophosphatemia can be caused by severe intestinal malabsorption, alcoholism, poor nutrition, and prolonged parenteral nutrition. Tenofovir therapy (tenofovir disoproxil fumarate more so than tenofovir alafamide) can cause renal phosphate wasting and hypophosphatemia. Severe hypophosphatemia can occur with refeeding after starvation. Hypophosphatemia can also be caused by chelation of phosphate in the gut by aluminum hydroxide antacids, calcium acetate (Phos-Lo), or sevelamer hydrochloride (Renagel). Excessive renal phosphate losses are also seen in proximal renal tubular acidosis, Fanconi syndrome, and in some women using oral contraceptives.

D. Aluminum Toxicity

Bone mineralization is inhibited by aluminum. Osteomalacia may occur in patients receiving long-term renal hemodialysis with tap water dialysate or from aluminum-containing antacids used to reduce phosphate levels.

E. Hypophosphatasia

Hypophosphatasia must not be confused with hypophosphatemia. Hypophosphatasia refers to a severe deficiency of bone alkaline phosphatase. It is a rare genetic cause of osteomalacia that is commonly misdiagnosed as osteoporosis.

F. Fibrogenesis Imperfecta Ossium

This rare condition sporadically affects middle-aged patients, who present with progressive bone pain and pathologic fractures. Bones have a dense “fishnet” appearance on radiographs. Serum alkaline phosphatase levels are elevated. Some patients have a monoclonal gammopathy, indicating a possible plasma cell dyscrasia causing an impairment in osteoblast function and collagen disarray.

Clinical Findings

Neonates and young children with hypocalcemia may have spasms and convulsions. Older children and adolescents can have bone pain and muscle weakness and may develop the skeletal deformities of classic rickets, such as delayed longitudinal growth, deformities at epiphyses leading to thickened wrists and ankles, and bowed legs or knock-knees (adolescents). Kyphoscoliosis or lumbar lordosis is common. Thickening at the costochondral joints can cause widening of the chest and deformities known as a “rachitic rosary.”

In adults, osteomalacia is initially asymptomatic. Then, nonspecific complaints that include fatigue, reduced endurance and muscle strength, and pain in the bones involving their shoulders ribs, low back, and thighs develop. Pathologic fractures can occur with little or no trauma.

Hypocalcemia causes a reduced quality of life, with fatigue, irritability, depression, anxiety, cognitive impairment, lethargy, and paresthesias in the circumoral area, hands, and feet. More severe manifestations include muscle weakness or cramps, carpopedal spasm, convulsions, tetany, laryngospasm, and stridor. Hypophosphatemia can cause severe major muscle weakness, reduced endurance, dysphagia, diplopia, cardiomyopathy, and respiratory muscle weakness. Patients may also have impaired cognition.

Diagnostic Tests

DXA BMD is used to determine the presence of low bone density that can be due to osteoporosis, osteomalacia, or both. Serum is obtained for calcium, albumin, phosphate, alkaline phosphatase, PTH, and 25-OHD determinations. Vitamin D *deficiency* is defined as a serum 25-OHD less than 20 ng/mL (50 nmol/L). Vitamin D *insufficiency* is defined as a serum 25-OHD between 20 ng/mL and 30 ng/mL (50–75 nmol/L). Patients in whom clinically severe osteomalacia develops typically have had chronic

severe vitamin D deficiency (serum 25-OHD under 12 ng/mL [25 nmol/L]).

1,25(OH)₂D₃ may be low even when 25(OH)D₂ levels are normal. In one series of biopsy-proved osteomalacia, alkaline phosphatase was elevated in 94% of patients; the calcium or phosphorus was low in 47% of patients; 25(OH)D₃ was low in 29% of patients; and urinary calcium was low in 18% of patients. Pseudofractures were seen in 18% of patients. Radiographs may show diagnostic features. Bone densitometry helps document the degree of osteopenia.

Oral contraceptives can cause renal hypophosphatemia in some women, so a drug holiday from oral contraceptives is warranted. Patients with otherwise unexplained hypophosphatemia should have a measurement of serum or plasma fibroblast growth factor 23 (FGF-23). Patients with high FGF23 levels can have genetic testing for X-linked hypophosphatemic rickets (*PHEX*), autosomal dominant hypophosphatemic rickets (*FGF23*), and autosomal recessive hypophosphatemic rickets (*DMP1*). In hypophosphatemic patients without such mutations, searching for a tumor causing tumor-induced osteomalacia is reasonable, particularly in patients with bone pain or fractures. Such tumors are typically small and may be located anywhere, so they are best localized using a whole-body DOTATATE-PET/CT scan.

Patients with apparent tumor-induced osteomalacia with hypophosphatemia require localization studies. Whole-body scanning with somatostatin analogs ⁶⁸Ga-DOTATOC PET/CT is the preferred imaging technique in this condition, detecting about 90% of tumors in small series.

Patients with hypophosphatasia have low serum levels of alkaline phosphatase (below 40 units/L in adults and below 20 units/L in severe cases). However, immediately following a fracture, serum alkaline phosphatase rises and may obscure the diagnosis. To confirm the diagnosis of hypophosphatasia in patients with a low serum alkaline phosphatase, a 24-hour urine is assayed for phosphoethanolamine, a substrate for tissue-nonspecific alkaline phosphatase whose excretion is always elevated in patients with hypophosphatasia. The diagnosis is further confirmed with genetic testing for mutations in the *ALPL* gene.

Differential Diagnosis

Osteomalacia often coexists with osteoporosis. The relative contribution of the two entities to diminished bone density may not be apparent until treatment, since a dramatic rise in bone density is often seen with therapy for osteomalacia. Phosphate deficiency must be distinguished from hypophosphatemia seen in hyperparathyroidism.

Prevention & Treatment

Humans naturally receive about 90% of their vitamin D from sunlight. To obtain adequate sunshine vitamin D, the face, arms, hands, or back must have sun exposure without sunscreen for 15 minutes at least twice weekly. In sunlight-deprived individuals (eg, veiled women, confined patients, or residents of higher latitudes during winter), vitamin D₃, 1000 international units daily, should be given prophylactically. Patients receiving long-term phenytoin therapy

should also receive vitamin D₃ supplementation. The main natural food source of vitamin D is fish, particularly salmon, mackerel, cod liver oil, and sardines or tuna canned in oil. Most commercial cow's milk is fortified with vitamin D at about 400 international units (10 mcg) per quart; however, yogurt and cottage cheese may contain little to no vitamin D₃.

Many vitamin supplements contain plant-derived vitamin D₂, which has variable biologic availability. Over-the-counter multivitamin/mineral supplements contain variable amounts of vitamin D, and vitamin D toxicity has occurred from two different multivitamins sold in the United States. Therefore, it is prudent to recommend that patients take a dedicated vitamin D₃ supplement from a reliable manufacturer.

Severe vitamin D deficiency can be treated with ergocalciferol (D₂), 50,000 international units orally once weekly for 8 weeks. Some patients require long-term supplementation with D₂ of up to 50,000 international units weekly. The danger of high-dose D₂ therapy is that some patients may mistakenly take it daily. The alternative is to treat vitamin D-deficient patients with daily cholecalciferol D₃ at doses of at least 2000 international units daily. The recommended maximum daily dose of vitamin D₃ is 10,000 international units/day for adults, with such high daily doses sometimes being required for patients with obesity, intestinal malabsorption, or following gastric bypass surgery. Some patients with severe malabsorption may require oral doses of 25,000–100,000 international units of vitamin D₃ daily. Patients with steatorrhea may respond better to oral 25(OH)D₃ (calcifediol), 50–100 mcg/day. Serum levels of 25-OHD should be monitored, and the dosage of vitamin D adjusted to maintain serum 25-OHD levels above 30 ng/mL. The Endocrine Society recommends a target range of serum 25-OHD of 40–60 ng/mL. Serum 25-OHD levels above this range provide no additional benefit and may actually cause *reduced* bone strength.

The addition of calcium supplements to vitamin D is probably not necessary for the prevention of osteomalacia in the majority of otherwise well-nourished patients. However, patients with malabsorption or poor nutrition should receive calcium supplementation: calcium citrate (eg, Citracal), 0.4–0.6 g elemental calcium per day, or calcium carbonate (eg, OsCal, Tums), 1–1.5 g elemental calcium per day. Calcium supplements are best administered with meals.

In hypophosphatemic rickets or osteomalacia, nutritional deficiencies are corrected, aluminum-containing antacids are discontinued, and patients with renal tubular acidosis are given bicarbonate therapy.

For patients with tumoral hypophosphatemia, resection of the tumor normalizes serum phosphate levels but about 20% experience recurrence, usually in the same location. With both tumoral and genetic FGF23-related hypophosphatemia, therapy with burosumab improves osteomalacia. For patients who cannot receive burosumab or who continue to have hypophosphatemia, oral phosphate supplements must be given long-term; oral phosphate causes diarrhea at higher doses, however, so many patients do not

achieve normal serum phosphate levels. Calcitriol, 0.25–0.5 mcg daily, is given to improve the impaired calcium absorption caused by the oral phosphate.

Patients with hypophosphatasia may be treated with asfotase alfa (Strensiq). Teriparatide can improve bone pain and fracture healing. Bisphosphonates are contraindicated.

Burt LA et al. Effect of high-dose vitamin D supplementation on volumetric bone density and bone strength: a randomized clinical trial. JAMA. 2019;322:736. [PMID: 31454046]

PAGET DISEASE OF BONE (Osteitis Deformans)



ESSENTIALS OF DIAGNOSIS

- ▶ Often asymptomatic.
- ▶ Bone pain may be the first symptom.
- ▶ Kyphosis, bowed tibias, large head, deafness, and frequent fractures.
- ▶ Serum calcium and phosphate normal; elevated alkaline phosphatase and urinary hydroxyproline.
- ▶ Dense, expanded bones on radiographs.

General Considerations

Paget disease of bone is manifested by one or more bony lesions having high bone turnover and disorganized osteoid formation. The involved bone first has increased osteoclast activity, causing lytic lesions in bone that may progress at about 1 cm/year. Increased osteoblastic activity follows, producing a high rate of disorganized bone formation. Involved bones become vascular, weak, and deformed. Eventually, there is a final burned-out phase with markedly reduced bone cell activity and abnormal bones that may be enlarged with skeletal deformity.

The prevalence of Paget disease has declined by about 36% over the past 20 years, yet it remains a common bone disease after osteopenia and osteoporosis. It is most common in the United Kingdom and in areas of European migration, and it is rare in Africa, India, Asia, and Scandinavia. In the United States, Paget disease is usually diagnosed in patients over age 40 years and affects about 1% of Whites over age 55 years, with its prevalence increasing with age. About 20% of cases are symptomatic; most cases are discovered incidentally during radiology imaging or because of incidentally discovered elevations in serum alkaline phosphatase.

Clinical Findings

A. Symptoms and Signs

Paget disease is often mild and asymptomatic. Only 27% of affected individuals are symptomatic at the time of diagnosis. Paget disease involves multiple bones (polyostotic) in 72% and only a single bone (monostotic) in 28%. It occurs

most commonly in the pelvis, vertebrae, femur, humerus, and skull. The affected bones are typically involved simultaneously, and the disease tends not to involve additional bones during its course. Pain, often described as aching and deep and worse at night, is the usual initial symptom. It may occur in the involved bone or in an adjacent joint, which can be involved with degenerative arthritis. Paget disease typically first affects long bones proximally and then advances distally, with bone pain at the osteolytic front being aggravated by weight bearing. Joint surfaces (such as the knee) can be involved and cause arthritic pain. The bones can become soft, leading to bowed tibias, kyphosis, and frequent “chalkstick” fractures with slight trauma. If the skull is involved, the patient may report headaches and an increased hat size; half such patients have dilated scalp veins, the “scalp vein sign.” Involvement of the petrous temporal bone frequently damages the cochlea and causes hearing loss (mixed sensorineural and conductive) and occasionally tinnitus or vertigo. Increased vascularity over the involved bones causes increased warmth and can cause vascular “steal” syndromes.

B. Laboratory Findings

Serum alkaline phosphatase is often markedly elevated and its source is bone (rather than liver). However, about 40% of patients with Paget disease of bone have normal serum alkaline phosphatase levels, particularly patients with monostotic involvement. Bone alkaline phosphatase is less useful for following the effectiveness of therapy. Other markers for bone turnover are serum N-terminal propeptide of type 1 collagen (NTx) and serum beta C-terminal propeptide of type 1 collagen (betaCTX). However, such bone turnover markers may overestimate or underestimate the response to treatment. Serum calcium may be elevated, particularly if the patient is at bed rest. A serum 25-OH vitamin D determination should be obtained to screen for vitamin D deficiency, which can also present with an increased serum alkaline phosphatase and bone pain.

C. Imaging

On radiographs, the initial lesions are typically osteolytic, with focal radiolucencies (“osteoporosis circumscripta”) in the skull or advancing flame-shaped lytic lesions in long bones. In vertebrae, the lesions of Paget disease may display a “clover” or “heart” appearance, helping distinguish them from bone metastases. Bone lesions may subsequently become sclerotic and have a mixed lytic and sclerotic appearance. The affected bones eventually become thickened and deformed. Technetium-99m pyrophosphate bone scans are helpful in delineating activity of bone lesions and finding additional lesions in other locations.

Differential Diagnosis

Rare familial types of sclerosing bone dysplasias share phenotypic homologies with Paget disease of bone. The differential diagnosis also includes myelofibrosis, intramedullary osteosclerosis, Erdheim-Chester disease, Langhans cell histiocytosis, and sickle cell disease.

Paget disease must be differentiated from primary bone lesions (eg, osteogenic sarcoma, plasma cell myeloma, and fibrous dysplasia) and from secondary bone lesions (eg, osteitis fibrosa cystica and metastatic carcinoma to bone). Fibrogenesis imperfecta ossium is a rare symmetric disorder that can mimic the features of Paget disease; serum alkaline phosphatase is likewise elevated. This condition may be associated with paraproteinemias.

Complications

If immobilization occurs, hypercalcemia and renal calculi may develop. With severe polyostotic disease, the increased vascularity may give rise to high-output heart failure. Arthritis frequently develops in joints adjacent to involved bone.

Extensive skull involvement may cause cranial nerve palsies from impingement of the neural foramina. Skull involvement can also cause a vascular steal syndrome with somnolence or ischemic neurologic events; the optic nerve may be affected, resulting in loss of vision. Jaw involvement can cause the teeth to spread intraorally and become misaligned. Vertebral collapse can cause compression of spinal cord or spinal nerves, resulting in radiculopathy or paralysis. Vertebral involvement can also cause a vascular steal syndrome with paralysis. Surgery for fractured long bones is often complicated by excessive blood loss from these vascular lytic lesions.

Rarely (less than 1%), a sarcoma or giant cell tumor develops in long-standing lesions. Sarcomatous change is suggested by a marked increase in bone pain, sudden rise in alkaline phosphatase, and appearance of a new lytic lesion.

Treatment

Asymptomatic patients may require only clinical surveillance. However, treatment with bisphosphonates should be considered for asymptomatic patients who have significant involvement of the skull, long bones, or vertebrae. Patients must be monitored carefully before, during, and after treatment with clinical examinations and serial serum alkaline phosphatase determinations.

Zoledronic acid is the treatment of choice. Administered intravenously as a single 5-mg dose, it normalizes the serum alkaline phosphatase in 89% of patients by 6 months and in 98% by 2 years.

Zoledronic acid should be administered prior to total arthroplasty for a Paget-involved joint or before osteotomy for lower extremity bowing in order to reduce the risk of intraoperative hemorrhaging and loosening of the prosthesis postoperatively. For patients with paraplegia due to vertebral involvement, intravenous zoledronic acid should be given while neurosurgical consultation is obtained.

Patients frequently experience a paradoxical increase in pain at sites of disease soon after commencing bisphosphonate therapy; this is the “first dose effect” and the pain usually subsides with further treatment. Following intravenous zoledronic acid, patients frequently experience fever, fatigue, myalgia, bone pain, and ocular problems. Serious side effects are rare but include seizures, uveitis, and acute

kidney disease. Asthma may occur in aspirin-sensitive patients. Hypocalcemia is common and may be severe, especially if intravenous bisphosphonates are given along with loop diuretics. Therefore, it is advisable to administer calcium and vitamin D supplements, especially during the first 2 weeks following treatment. Any vitamin D deficiency should be corrected before prescribing a bisphosphonate.

Oral bisphosphonate regimens are inferior to intravenous zoledronic acid for therapy of Paget disease. However, if they are given, to prevent esophageal complications, oral bisphosphonates should be taken with 8 oz of plain water only, and the patient must remain upright afterward. Oral bisphosphonates are relatively contraindicated in patients with a history of esophagitis, esophageal stricture, dysphagia, hiatal hernia, or achalasia. Patients who cannot tolerate bisphosphonates may be treated with calcitonin.

► Prognosis

The prognosis is good, but relapse can occur after an initial successful treatment with bisphosphonate. By 6.5 years after initial therapy, the recurrence rate is 12.5% after treatment with zoledronic acid and 62% after risedronate. Patients must be monitored long term, measuring serum alkaline phosphatase at least yearly. In general, the prognosis is worse the earlier in life the disease starts. Fractures usually heal well. In the severe forms, marked deformity, intractable pain, and high-output heart failure occur if not treated with bisphosphonates. Osteosarcoma that arises at sites of Paget disease results in a 2-year survival of only 25%.

Hsu E. Paget's disease of bone: updates for clinicians. *Curr Opin Endocrinol Diabetes Obes.* 2019;26:329. [PMID: 31574000]

Kuźnik A et al. Bisphosphonates—much more than only drugs for bone diseases. *Eur J Pharmacol.* 2020;866:172773. [PMID: 31705903]

Ralston SH et al. Diagnosis and management of Paget's disease of bone in adults: a clinical guideline. *J Bone Miner Res.* 2019; 34:579. [PMID: 30803025]

- Elevated plasma ACTH level; cosyntropin unable to stimulate serum cortisol to ≥ 20 mcg/dL (550 nmol/L).

- **Acute adrenal crisis:** above manifestations become critical, with fever, shock, confusion, coma, death.

► General Considerations

Primary adrenal insufficiency (Addison disease) is caused by dysfunction or absence of the adrenal cortices. Secondary adrenal insufficiency is caused by deficient secretion of ACTH.

Addison disease is an uncommon disorder. In the United States, the prevalence is about 90–140 cases per million and the annual incidence is about 5–6 cases per million. Addison disease refers to a chronic deficiency of cortisol caused by adrenocortical insufficiency; plasma ACTH and alpha-MSH levels are consequently elevated, causing pigmentation that ranges from none to strikingly dark. Patients with destruction of the adrenal cortices or with classic 21-hydroxylase deficiency also have mineralocorticoid deficiency, typically with hyponatremia, volume depletion, and hyperkalemia. In contrast, mineralocorticoid deficiency is not present in patients with familial corticosteroid deficiency, Allgrove syndrome, or secondary adrenal insufficiency.

Acute adrenal (Addisonian) crisis is an emergency caused by insufficient cortisol. Crisis may occur in the course of treatment of chronic adrenal insufficiency, or it may be the presenting manifestation of adrenal insufficiency. Acute adrenal crisis is more commonly seen in primary adrenal insufficiency than in secondary adrenal insufficiency. It is usually precipitated by one of the following: (1) Severe stress (eg, infection, trauma, surgery, hyperthyroidism, or prolonged fasting), or minor stress (vaccinations) in patients with latent or treated adrenal insufficiency; (2) Hyperthyroidism or prescription of thyroid hormone to patients with untreated adrenal insufficiency; (3) Nonadherence to glucocorticoid replacement or sudden withdrawal of adrenocortical hormone in patients with chronic primary or secondary adrenal insufficiency; (4) Bilateral adrenalectomy or removal of a functioning adrenal tumor that had suppressed the other adrenal gland; (5) Sudden destruction of the pituitary gland (pituitary necrosis) or damage to both adrenals (by trauma, hemorrhage, anticoagulant therapy, thrombosis, infection or, rarely, metastatic carcinoma); (6) Administration of intravenous etomidate (used for rapid anesthesia induction or intubation).

► Etiology

Autoimmunity is the most common cause of Addison disease in industrialized countries, accounting for about 90% of spontaneous cases; adrenal function decreases over several years as it progresses to overt adrenal insufficiency. Over half the cases of autoimmune Addison disease occur as part of an autoimmune polyendocrine syndrome (APS-1, APS-2). Addison disease can also occur following

DISEASES OF THE ADRENAL CORTEX

PRIMARY ADRENAL INSUFFICIENCY (Addison Disease)



ESSENTIALS OF DIAGNOSIS

- Deficiency of cortisol and mineralocorticoid from destruction of the adrenal cortex.
- Weakness, vomiting, diarrhea; abdominal pain, arthralgias; amenorrhea.
- Increased skin pigmentation, especially of creases, pressure areas, and nipples.
- Hypovolemic hypotension, small heart.
- **Hyponatremia;** hyperkalemia (may be absent with vomiting and diarrhea); hypoglycemia; eosinophilia.

treatment for malignancies with PD-1 immune checkpoint inhibitors.

Bilateral adrenal infiltrative diseases cause primary adrenal insufficiency. Causative neoplasms include lymphomas, breast cancer, and lung cancer. Causative infections include tuberculosis, coccidiomycosis, histoplasmosis, cytomegalovirus, cryptococcus, and syphilis.

Infections of the adrenal glands, particularly with cytomegalovirus, are found in nearly half of patients with untreated HIV at autopsy. However, a much lower percentage have clinical Addison disease. The diagnosis of adrenal insufficiency in HIV patients is often problematic. A cortisol resistance syndrome has been described in patients with HIV, and a revision of normal range for the cosyntropin test for these patients has been advocated (normal peak cortisol over 22 mcg/dL). Also, isolated hyperkalemia occurs commonly in HIV patients, particularly during therapy with pentamidine; this is usually due to isolated hypoaldosteronism and responds to mineralocorticoid (fludrocortisone) therapy alone.

Bilateral adrenal hemorrhage may occur with sepsis, heparin-associated thrombocytopenia, anticoagulation, or the antiphospholipid antibody syndrome. It may occur in association with major surgery or trauma, presenting about 1 week later with pain, fever, and shock. It may also occur spontaneously and present with flank pain. Meningococcemia may be associated with purpura and adrenal insufficiency secondary to adrenal infarction (Waterhouse-Friderichsen syndrome).

Adrenoleukodystrophy is an X-linked peroxisomal disorder causing accumulation of very long-chain fatty acids in the adrenal cortex, testes, brain, and spinal cord. Adrenal insufficiency ultimately occurs in 80% of affected patients and accounts for one-third of cases of Addison disease in boys. It presents most commonly in childhood or adolescence but can manifest at any age.

Congenital adrenal insufficiency occurs in several conditions. Familial corticosteroid deficiency is an autosomal recessive disease that is caused by mutations in the adrenal ACTH receptor (melanocortin 2 receptor, MC2R). It is characterized by isolated cortisol deficiency and ACTH resistance and may present with neonatal hypoglycemia, frequent infections, and dark skin pigmentation. Triple A (Allgrove) syndrome is caused by a mutation in the AAAS gene that encodes a protein known as ALADIN (*alachrima, achalasia, adrenal insufficiency, neurologic disorder*). Cortisol deficiency usually presents in infancy but may not occur until the third decade of life.

Congenital adrenal hyperplasia is caused by various genetic defects in the enzymes responsible for steroid synthesis. Due to defective cortisol synthesis, patients have variable degrees of adrenal insufficiency and increased levels of ACTH that causes hyperplasia of the adrenal cortex. The most common enzyme defect is *P450c21* (*21-hydroxylase deficiency*).

Drugs that cause primary adrenal insufficiency include mitotane, abiraterone acetate, and the tyrosine kinase inhibitors lenvatinib and vandetanib. **Rare causes** of adrenal insufficiency include lymphoma, metastatic carcinoma, scleroderma, amyloidosis, and hemochromatosis.

Clinical Findings

A. Symptoms and Signs

The onset of symptoms can occur suddenly but usually develops gradually over months or years. The diagnosis is often delayed, since many early symptoms are nonspecific. Over 90% of patients complain of fatigue, reduced stamina, weakness, anorexia, and weight loss. Over 80% of affected patients present with symptoms of orthostatic hypotension (aggravated by dehydration caused by nausea or vomiting), lightheadedness with standing, salt craving, and eventually hyperpigmentation of skin and gums. Abdominal pain, nausea, and vomiting eventually develop in most patients; diarrhea can occur, aggravating dehydration and hypotension. Fevers and lymphoid tissue hyperplasia may also occur. Patients often have significant pain: arthralgias, myalgias, chest pain, abdominal pain, back pain, leg pain, or headache.

Psychiatric symptoms include anxiety, irritability and depression; by the time of diagnosis, over 40% of patients have been told that their symptoms were psychological. Cerebral edema can cause headache, vomiting, gait disturbance, and intellectual dysfunction that may progress to coma. Hypoglycemia can occur and worsen the patient's weakness and mental functioning. Patients treated long-term for adrenal insufficiency appear to be more prone to pneumonia and gastrointestinal and urinary tract infections.

Hyperpigmentation of the skin and gums eventually occurs in most patients with Addison disease and is caused by increased pituitary secretion of alpha-MSH (melanocyte-stimulating hormone). Skin hyperpigmentation varies among affected patients (eg, from none to increased freckling to diffuse darkening that resembles a suntan or a bronze appearance). Sun-exposed areas darken the most, but nonexposed areas darken as well. Hyperpigmentation is often especially prominent over the knuckles, elbows, knees, posterior neck, palmar creases, gingival mucosa, and vermillion border of the lips. Nail beds may develop longitudinal pigmented bands. Nipples and areolas tend to darken. The skin also darkens in pressure areas, such as the belt or brassiere lines and the buttocks. Skin folds and new scars may also become pigmented. Conversely, patches of autoimmune vitiligo can be found in about 10% of patients. Scant axillary and pubic hair typically develops in women.

In pregnancy, undiagnosed adrenal insufficiency is rare, since the condition tends to cause anovulation and reduced fertility. In the first trimester, symptoms such as fatigue, nausea, vomiting, abdominal pain, and orthostasis are typically attributed to the pregnancy, thus delaying the diagnosis. Worse, the increased skin pigmentation of adrenal insufficiency may be mistaken for chloasma (melasma). Undiagnosed adrenal insufficiency can cause intrauterine growth retardation and fetal loss. Pregnant women with undiagnosed adrenal insufficiency can experience shock from adrenal crisis, particularly during the first trimester, concurrent illness, labor, or postpartum.

Patients with preexisting type 1 diabetes experience more frequent hypoglycemia with the onset of adrenal insufficiency, such that their insulin dosage must be reduced.

Acute adrenal crisis is an immediate threat to life. Affected patients have magnified symptoms of chronic

adrenal insufficiency and experience an acute deterioration in their health, typically with acute gastrointestinal symptoms and fever that can mimic an abdominal emergency. Infections (lower respiratory, urinary, or gastrointestinal) are common triggers for acute adrenal crisis. Patients also frequently experience back pain, arthralgias, and profound fatigue. They may have delirium or coma, sometimes aggravated by hypoglycemia. Adrenal crisis is marked by orthostatic dizziness and hypotension (blood pressure below 100 mm Hg systolic or 20 mm Hg lower than their baseline). **Reversible cardiomyopathy and heart failure can also occur, causing hypotension that can progress to life-threatening shock that does not respond to intravenous fluids and vasopressors.**

B. Laboratory Findings

Typically there is mild anemia, **moderate neutropenia, lymphocytosis, and eosinophilia** (total eosinophil count over 300/mCL). Among patients with chronic adrenal insufficiency, the serum sodium is usually low (38%) and the potassium usually elevated (64%). However, patients with vomiting or diarrhea may not be hyperkalemic. Fasting hypoglycemia is common. Hypercalcemia may be present.

A plasma cortisol less than 3 mcg/dL (83 nmol/L) at 8 AM is diagnostic, especially if accompanied by simultaneous elevation of the plasma ACTH level greater than 200 pg/mL (44 pmol/L). The diagnosis is confirmed by a simplified cosyntropin stimulation test. (1) Synthetic ACTH₁₋₂₄ (cosyntropin), 0.25 mg, is given intramuscularly. (2) Serum cortisol is obtained 45 minutes after cosyntropin is administered. Normally, serum cortisol rises to at least 20 mcg/dL (550 pmol/L), whereas patients with adrenal insufficiency have stimulated serum cortisol levels **less than 20 mcg/dL (550 pmol/L)**. For patients receiving corticosteroid treatment, **hydrocortisone must not be given for at least 8 hours before the test**. Other corticosteroids (eg, prednisone, dexamethasone) do not interfere with specific assays for cortisol. Cosyntropin is usually well tolerated, but infrequent (less than 5%) side effects have included hypersensitivity reactions with nausea, headache, dizziness, dyspnea, palpitations, flushing, edema, and local injection site reactions. Cosyntropin may be administered during pregnancy; however, the test may lack sensitivity, since adrenal ACTH-responsiveness increases during pregnancy.

Serum DHEA levels are less than 1000 ng/mL (350 nmol/L) in 100% of patients with adrenal insufficiency but also in about 15% of the population, so the test is very sensitive but not specific.

One or more serum anti-adrenal antibodies are found in about 50% of cases of autoimmune Addison disease. The sensitivity of four serum anti-adrenal antibodies is as follows: cytoplasmic antibodies (26%), 21-hydroxylase antibodies (21%), 17-hydroxylase antibodies (21%), and side-chain cleavage antibodies (16%). Antibodies to thyroid (45%) and other tissues may also be present.

Elevated plasma renin activity (PRA) indicates the presence of depleted intravascular volume and the need for fludrocortisone administration. Serum epinephrine levels are low in untreated patients with adrenal insufficiency.

Salt-wasting congenital adrenal hyperplasia due to 21-hydroxylase deficiency is usually diagnosed at birth in females due to ambiguous genitalia. Males and patients with milder enzyme defects may present later. The diagnosis of adrenal insufficiency is made as above. The specific diagnosis requires elevated serum levels of 17-OH progesterone.

Young men with idiopathic Addison disease are screened for X-linked adrenoleukodystrophy by determining plasma very long-chain fatty acid levels; affected patients have high levels.

In acute adrenal crisis, blood, sputum, or urine cultures may be positive if bacterial infection is the precipitating cause.

C. Imaging

When adrenal insufficiency is not clearly autoimmune, a CT scan of the adrenal glands should be obtained. Small, noncalcified adrenals are seen in autoimmune Addison disease. The adrenals are enlarged in about 85% of cases related to metastatic or granulomatous disease. Adrenal calcifications occur in about 50% of cases of tuberculous Addison disease but are also seen with hemorrhage, fungal infection, pheochromocytoma, and melanoma.

Differential Diagnosis

Patients with ACTH deficiency have normal mineralocorticoid production and do not develop hyperkalemia. Patients with secondary adrenal insufficiency (see Hypopituitarism) lack ACTH and have normal to decreased skin pigmentation that has been described as "alabaster skin." This contrasts with the increased skin pigmentation in patients with Addison disease. Hemochromatosis also causes bronze skin hyperpigmentation, and hemochromatosis may in fact be the cause of Addison disease. Acute adrenal crisis must be distinguished from other causes of shock (eg, septic, hemorrhagic, cardiogenic).

The constitutional symptoms may be mistaken for cancer, anorexia nervosa, or emotional stress. Acute adrenal insufficiency must be distinguished from an acute abdomen in which neutrophilia is the rule, whereas in adrenal insufficiency there is lymphocytosis and eosinophilia. The neurologic manifestations of Allgrove syndrome and adrenoleukodystrophy (especially in women) may mimic multiple sclerosis. Hyperkalemia can be caused by hyporeninemic hypoaldosteronism from type IV renal tubular acidosis. Hyperkalemia is also seen with gastrointestinal bleeding, rhabdomyolysis, hyperkalemic paralysis, and some drugs (eg, angiotensin-converting enzyme [ACE] inhibitors, spironolactone, and dapsone) (see Chapter 21).

Hyponatremia is seen in many other conditions (eg, hypothyroidism, diuretic use, heart failure, cirrhosis, vomiting, diarrhea, severe illness, or major surgery) (see Figure 21-1). Nearly 40% of critically ill patients have low serum cortisol levels due to low serum albumin levels; their total serum cortisol levels may be low but their serum free cortisol levels are normal.

► Complications

Any of the complications of the underlying disease (eg, tuberculosis) are more likely to occur in adrenal insufficiency, and intercurrent infections may precipitate an acute adrenal crisis. Associated autoimmune diseases are common (see above).

► Treatment

A. General Measures

Patients and family members must be thoroughly educated about adrenal insufficiency. *Patients are advised to wear a medical alert bracelet or medal reading, "Adrenal insufficiency—takes hydrocortisone."* They need to be provided with a dose escalation schedule for increased corticosteroids for illness, accidents, or prior to minor surgical procedures and for increased fludrocortisone for hot weather or prolonged strenuous exercise. Corticosteroids and fludrocortisone must be prescribed in liberal amounts with automatic refills to avoid the patient's running out of medication. It is also advisable to prescribe a routine antiemetic such as ondansetron ODT 8-mg tablets to be taken every 8 hours for nausea. Parenteral hydrocortisone (Solu-Cortef) 100 mg is also prescribed for patient self-injection in the event of vomiting. Patients must receive advance instructions to seek medical attention at an emergency facility immediately in the event of vomiting or severe illness. All infections should be treated immediately and vigorously, with hydrocortisone administered at appropriately increased doses.

B. Specific Therapy

Replacement therapy should include corticosteroids with mineralocorticoids for primary adrenal insufficiency. In mild cases, corticosteroids alone may be adequate.

1. Corticosteroid replacement therapy—Maintenance therapy for most patients with Addison disease is 15–30 mg of hydrocortisone orally daily in two or three divided doses (eg, 10 mg at 7 AM, 10 mg at 1 PM, and 5 mg at 7 PM). Some patients respond better to prednisone or methylprednisolone in doses of about 3–6 mg daily in divided doses. Adjustments in dosage are made according to the clinical response. The corticosteroid dose should be kept at the lowest level at which the patient feels clinically well.

Patients with partial ACTH deficiency (basal morning serum cortisol above 8 mg/dL [220 nmol/L]) require hydrocortisone replacement in lower doses of about 5 mg orally twice daily or even 10 mg every morning. Some patients feel better with the substitution of prednisone (2–7.5 mg/day orally) or methylprednisolone (2–6 mg/day orally), given in divided doses. Fludrocortisone is not required. Additional corticosteroid must be given during stress, (eg, infection, trauma, or surgical procedures). For mild illness or mild-moderate surgical stress, corticosteroid doses are doubled or tripled. **For severe illness, trauma, or major surgical stress, hydrocortisone 100 mg is given intravenously, followed by 200 mg daily, given as either a continuous intravenous infusion or as 50 mg boluses given every 6 hours**

intravenously or intramuscularly and then reduced to usual doses as the stress subsides.

Patients with secondary adrenal insufficiency due to treatment with corticosteroids require their usual daily dose of corticosteroid during minor surgery and mild illness; supplemental hydrocortisone is required for major surgeries or illness.

Plenadren MR (5- or 20-mg modified-release tablets) is a once-daily dual-release oral preparation of hydrocortisone that may be administered in the morning (usual dose range is 20–30 mg daily). Preliminary studies indicate that plenadren may improve quality of life in some patients with adrenal insufficiency. It is not available in the United States but is available in Canada and elsewhere.

To determine the optimal corticosteroid replacement dosage, it is necessary to monitor patients carefully for clinical signs of over- or under-replacement. A proper corticosteroid dose usually results in clinical improvement. A white blood cell (WBC) count with a differential can be useful, since a relative neutrophilia and lymphopenia can indicate corticosteroid over replacement, and vice versa. Serum ACTH levels vary substantially and should not be used to determine dosing.

Caution: Increased corticosteroid dosing is required in circumstances of infection, trauma, surgery, stressful diagnostic procedures, or other forms of stress. Rifampin use increases the clearance of hydrocortisone and necessitates increased dosing of hydrocortisone by up to 50%. During the third trimester of pregnancy, corticosteroid requirements are higher, so usual corticosteroid doses are increased by 50%. For severe stress of major illness, surgery, or delivery, a maximum stress dose of hydrocortisone is given as 50–100 mg intravenously or intramuscularly, followed by 50 mg every 6 hours (continuous intravenous infusion or boluses), then reduced over several days. However, following major trauma, increased doses of replacement hydrocortisone may be required for up to several weeks. Lower doses, oral or parenteral, are used for less severe stress. For immunizations that are given with an adjuvant, such as varicella zoster (Shingrix), there is sufficient local inflammation that increased doses of hydrocortisone are recommended for 5 days following the immunization. The dose is reduced back to normal as the stress subsides. Decreased corticosteroid dosing is required when medications are prescribed that inhibit corticosteroid metabolism by blocking the isoenzyme CYP3A4, particularly the antifungals ketoconazole or itraconazole, the antidepressant nefazodone, anti-HIV protease inhibitors, and cobicistat.

2. Mineralocorticoid replacement therapy—Fludrocortisone acetate has a potent sodium-retaining effect. The dosage is 0.05–0.3 mg orally daily or every other day. In the presence of postural hypotension, hyponatremia, or hyperkalemia, the dosage is increased. Similarly, in patients with fatigue, an elevated PRA indicates the need for a higher replacement dose of fludrocortisone. If edema, hypokalemia, or hypertension ensues, the dose is decreased. During treatment with hydrocortisone with maximum doses appropriate for stress, fludrocortisone replacement is not

required. Some patients cannot tolerate fludrocortisone and must substitute NaCl tablets to replace renal sodium loss.

3. DHEA replacement therapy—DHEA is given to some women with adrenal insufficiency. In a double-blind clinical trial, women taking DHEA 50 mg orally each morning experienced an improved sense of well-being, increased muscle mass, and a reversal in bone loss at the femoral neck. DHEA replacement did not improve fatigue, cognitive problems, or sexual dysfunction; however, its placebo effect may be significant in that regard. Older women who receive DHEA should be monitored for androgenic effects. Because over-the-counter preparations of DHEA have variable potencies, it is best to have the pharmacy formulate this with pharmaceutical-grade micronized DHEA.

4. Treatment of hyperandrogenism in women with congenital adrenal hyperplasia

—See Hirsutism & Virilization.

5. Treatment of acute adrenal crisis—If acute adrenal crisis is suspected but the diagnosis of adrenal insufficiency is not yet established, intravenous access must be established. Blood is drawn for cultures, plasma ACTH, serum cortisol, serum glucose, BUN, creatinine, and electrolyte levels. A urinalysis is obtained to screen for a urinary tract infection. Without waiting for the results, treatment is initiated *immediately* with hydrocortisone, 100 mg by intravenous bolus followed by 50 mg intravenously every 6 hours as either intravenous boluses or a continuous intravenous infusion. The hydrocortisone dosage may then be reduced according to the clinical picture and laboratory test results.

Intravenous fluids are administered as either 0.9% normal saline or 0.9% normal saline/5% dextrose solutions. A volume of 2–3 L is given quickly and then the intravenous rate is reduced according to clinical parameters and frequent serum electrolytes and glucose determinations. When intravenous saline is stopped, mineralocorticoid replacement is commenced with fludrocortisone, starting with 0.1 mg orally daily and adjusted according to serum electrolyte determinations.

Since bacterial infection frequently precipitates acute adrenal crisis, broad-spectrum antibiotics should be administered empirically while waiting for the results of initial cultures (Table 30–5). The patient must also be treated for electrolyte abnormalities, hypoglycemia, and dehydration, as indicated.

When the patient is able to take food by mouth, hydrocortisone is administered orally in doses of 10–20 mg every 6 hours, and the dosage is reduced to maintenance levels as needed. Most patients ultimately require hydrocortisone twice daily (10–20 mg in the morning; 5–10 mg in the evening). Mineralocorticoid replacement is not needed when large amounts of hydrocortisone are given, but as its dose is reduced, it is usually necessary to add fludrocortisone acetate, 0.05–0.2 mg orally daily. Some patients never require fludrocortisone or become edematous at doses of more than 0.05 mg once or twice weekly. Once the crisis has passed, the patient must be evaluated to assess the degree of permanent adrenal insufficiency and to establish the cause, if possible.

► Prognosis

The life expectancy of patients with Addison disease is reasonably normal, as long as they are compliant with their medications and knowledgeable about their condition. However, one retrospective Swedish study of 1675 patients with Addison disease found an unexpected increase in all-cause mortality, mostly from cardiovascular disease, malignancy, and infection. Adrenal crisis can occur in patients who stop their medication or who experience stress such as infection, trauma, or surgery without appropriately higher doses of corticosteroids. Patients who take excessive doses of corticosteroid replacement can develop Cushing syndrome, which imposes its own risks.

Some patients feel residual fatigue, despite corticosteroid and mineralocorticoid replacement. This may be due, in part, to the inadequacy of oral replacement to duplicate cortisol's normal circadian rhythm. Also, patients with Addison disease are deficient in epinephrine, but replacement epinephrine is not available. Fatigue may also be an indication of suboptimal dosing of medication, electrolyte imbalance, or concurrent hypothyroidism or diabetes mellitus.

Rapid treatment is usually lifesaving in acute adrenal crisis. However, if adrenal crisis is unrecognized and untreated, shock that is unresponsive to fluid replacement and vasopressors can result in death.

Merke DP et al. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *N Engl J Med*. 2020;383:124861. [PMID: 32966723]

Prete A et al. Prevention of adrenal crisis: cortisol responses to major stress compared to stress dose hydrocortisone delivery. *J Clin Endocrinol Metab*. 2020;105:2262. [PMID: 32170323]

Rushworth RL et al. Adrenal crisis. *N Engl J Med*. 2019;381:852. [PMID: 31461595]

Saverino S et al. Autoimmune Addison's disease. *Best Pract Res Clin Endocrinol Metab*. 2020;34:101379. [PMID: 32063488]

CUSHING SYNDROME (Hypercortisolism)

ESSENTIALS OF DIAGNOSIS

- Central obesity, muscle wasting, hirsutism, purple striae.
- Psychological changes.
- Osteoporosis, hypertension, poor wound healing.
- Hyperglycemia, leukocytosis, lymphocytopenia, hypokalemia.
- Elevated serum cortisol and urinary free cortisol. Lack of normal suppression by dexamethasone.

► General Considerations

The term Cushing "syndrome" refers to the manifestations of excessive corticosteroids, commonly due to supraphysiologic doses of corticosteroid drugs and rarely due to

spontaneous production of excessive cortisol by the adrenal cortex. Cases of spontaneous Cushing syndrome are rare, with an incidence of 2.6 new cases yearly per million population in the United States.

A. Cushing Disease with Elevated ACTH Levels

About 68% of cases are due to Cushing “disease,” caused by a benign ACTH-secreting pituitary adenoma that is typically smaller than 5 mm and usually located in the anterior pituitary (94%); however, about 6% of such adenomas are ectopic in locations such as the cavernous sinus, sphenoid sinus, ethmoid sinus, or posterior pituitary. Cushing disease is at least three times more frequent in women than men.

About 7% of cases are due to nonpituitary ACTH-secreting neuroendocrine neoplasms that produce ectopic ACTH. Ectopic locations include the lungs (55%), pancreas (9%), mediastinum-thymus (8%), adrenal (6%), gastrointestinal tract (5%), thyroid (4%), and other sites (13%). About 15% of cases are due to ACTH from a source that cannot be initially located.

B. Cushing Disease with Normal or Low ACTH

About 25% of cases are due to excessive autonomous secretion of cortisol by the adrenals. Cortisol secretion is independent of ACTH, and plasma ACTH levels are usually low or low-normal. Most such cases are due to a unilateral adrenal tumor. Benign adrenal adenomas are generally small and produce mostly cortisol; adrenocortical carcinomas are usually large when discovered and can produce excessive cortisol as well as androgens but may be nonsecretory. ACTH-independent macronodular adrenal hyperplasia can also produce hypercortisolism due to the adrenal cortex cells’ abnormal stimulation by hormones such as catecholamines, arginine vasopressin, serotonin, hCG/LH, or gastric inhibitory polypeptide; in the latter case, hypercortisolism may be intermittent and food-dependent, and plasma ACTH levels may not be completely suppressed. Bilateral primary pigmented adrenal macronodular adrenocortical disease may be an isolated condition or part of the Carney complex, an autosomal dominant condition with additional features consisting of myxomas of the heart and skin with spotty skin pigmentation and facial freckles.

► Clinical Findings

A. Symptoms and Signs

The manifestations of Cushing syndrome vary considerably. Early in the course of the disease, patients frequently complain of nonspecific symptoms, such as fatigue or reduced endurance but may have few, if any, of the physical stigmata described below. Most patients eventually develop central obesity with a plethoric “moon face,” “buffalo hump,” supraclavicular fat pads, protuberant abdomen, and thin extremities. Muscle atrophy causes weakness, with difficulty standing up from a seated position or climbing stairs. Patients may also experience backache, headache, hypertension, osteoporosis, avascular necrosis of bone, acne, superficial skin infections, and oligomenorrhea or amenorrhea in women or erectile dysfunction in men.

Patients may have thirst and polyuria (with or without glycosuria), renal calculi, glaucoma, purple striae (especially around the thighs, breasts, and abdomen), and easy bruising. Unusual bacterial or fungal infections are common. Wound healing is impaired. Mental symptoms may range from diminished ability to concentrate to increased lability of mood to frank psychosis. Patients are susceptible to opportunistic infections. Hyperpigmentation is common with ectopic ACTH-secreting neoplasms that tend to produce very high plasma ACTH levels; hyperpigmentation is uncommon with pituitary Cushing disease.

Adrenal carcinomas usually have gross metastases by the time of diagnosis. Microscopic metastases are not visible by scanning but can be inferred from the presence of detectable cortisol levels following removal of the primary adrenal tumor in patients with a cortisol-secreting carcinoma and Cushing syndrome. The ENSAT staging system is used: stage 1 is a localized tumor 5 cm or smaller; stage 2, a localized tumor larger than 5 cm; stage 3, tumor with local metastases; and stage 4, tumor with distant metastases.

B. Laboratory Findings

Glucose tolerance is impaired as a result of insulin resistance. Polyuria is present as a result of increased free water clearance; diabetes mellitus with glycosuria may worsen it. Patients with Cushing syndrome often have leukocytosis with relative granulocytosis and lymphopenia. Hypokalemia may be present, particularly in cases of ectopic ACTH secretion.

1. Diagnostic tests for hypercortisolism—Testing for hypercortisolism involves determining whether the following characteristics of Cushing syndrome are present: (1) lack of cortisol diurnal variation, (2) reduced suppressibility of cortisol by dexamethasone, (3) increased cortisol production rate, and (4) suppression of plasma ACTH by hypercortisolism from an adrenal nodule. Conflicting results are common.

Late-night (10–11 PM) salivary cortisol determinations are particularly useful, especially for ACTH-dependent hypercortisolism. Late-night salivary cortisol levels are normally 150 ng/dL (4.0 nmol/L) or less. Late-night salivary cortisol levels that are consistently greater than 250 ng/dL (7.0 nmol/L) are considered very abnormal. The late-night salivary cortisol test has a relatively high sensitivity and specificity for Cushing syndrome.

The **overnight dexamethasone suppression test** is an easy screening test for hypercortisolism and is particularly sensitive for mild ACTH-independent hypercortisolism from an adrenal nodule. Dexamethasone 1 mg is given orally at 11 PM and serum is collected for cortisol determination at 8 AM the next morning; a cortisol level less than 1.8 mcg/dL (50 nmol/L, high-performance liquid chromatography [HPLC] assay) excludes Cushing syndrome with some certainty. However, 8% of established patients with pituitary Cushing disease have dexamethasone-suppressed cortisol levels less than 2 mcg/dL (55 nmol/L). Antiseizure drugs (eg, phenytoin, phenobarbital, primidone) and rifampin accelerate the metabolism of dexamethasone,

causing a lack of cortisol suppression by dexamethasone. Estrogens—during pregnancy or as oral contraceptives or HRT—may also cause lack of dexamethasone suppressibility.

A **24-hour urinary free cortisol and creatinine** is usually used to confirm hypercortisolism in patients with a high late-night salivary cortisol or an abnormal dexamethasone suppression test. A high 24-hour urine free cortisol (greater than 50 mcg/day or 140 nmol/day in adults), or free cortisol to creatinine ratio of greater than 95 mcg cortisol/g creatinine, helps confirm hypercortisolism. However, many patients with mild hypercortisolism have a urinary free cortisol that is misleadingly within the reference range when measured by liquid chromatography-tandem mass spectrometry. A misleadingly high urine free cortisol excretion occurs with high fluid intake. In pregnancy, urine free cortisol is increased, while 17-hydroxycorticosteroids remain normal and diurnal variability of serum cortisol is normal. Carbamazepine and fenofibrate cause false elevations of urine free cortisol when determined by HPLC.

2. Diagnostic tests for the source of hypercortisolism—

Once hypercortisolism is confirmed, a plasma ACTH and plasma DHEAS are obtained. A plasma ACTH below 6 pg/mL (1.3 pmol/L), with a low serum DHEAS, indicates a probable adrenal tumor, whereas higher levels are produced by pituitary or ectopic ACTH-secreting tumors. Certain ACTH assays suffer interference and report low-normal plasma ACTH levels in patients with ACTH-independent hypercortisolism. Serum dehydroepiandrosterone sulfate (DHEAS) levels can be used as a proxy for ACTH, since DHEAS secretion is ACTH-dependent; levels below the reference range and particularly below 40 mcg/dL (1.1 nmol/L) imply ACTH-independent hypercortisolism.

C. Imaging

In **ACTH-independent Cushing syndrome**, CT of the adrenals usually detects a mass lesion, which is most often an adrenal adenoma. Adrenocortical carcinomas can usually be distinguished from benign adrenal adenomas since they are generally larger (average 11 cm) and many have metastases that are visible on preoperative scans.

In **ACTH-dependent Cushing syndrome**, MRI of the pituitary gland demonstrates a pituitary lesion in about 50% of cases. Premature cerebral atrophy is often noted. When the pituitary MRI is normal or shows a tiny (less than 5 mm) irregularity that may be incidental, selective catheterization of the inferior petrosal sinus veins draining the pituitary is performed. ACTH levels in the inferior petrosal sinus that are more than twice the simultaneous peripheral venous ACTH levels are indicative of pituitary Cushing disease. Inferior petrosal sinus sampling is also done during ovine CRH (oCRH or Acthrel) administration, which ordinarily causes the ACTH levels in the inferior petrosal sinus to be over three times the peripheral ACTH level when the pituitary gland is the source of ACTH.

When inferior petrosal sinus ACTH concentrations are not above the requisite levels, a search for an ectopic source of ACTH is undertaken. Location of ectopic sources of

ACTH begins with CT scanning of the chest and abdomen, with special attention to the lungs (for carcinoid or small cell carcinomas), the thymus, the pancreas, and the adrenals. In patients with ACTH-dependent Cushing syndrome, chest masses should not be assumed to be the source of ACTH, since opportunistic infections are common. It is prudent to biopsy a chest mass to confirm the pathologic diagnosis prior to resection.

For Cushing syndrome due to ectopic ACTH, CT scanning fails to detect the source of ACTH in about 34% of cases. In such cases, the most sensitive (82%) scanning technique is whole-body imaging with ⁶⁸Ga-somatostatin receptor-PET/CT (⁶⁸Ga-DOTATATE-PET/CT). The next most sensitive (58%) scanning technique is whole-body imaging with ¹⁸F-DOPA-PET/CT.

► Differential Diagnosis

Alcoholic patients can have hypercortisolism and many clinical manifestations of Cushing syndrome. Pregnant women have elevated serum ACTH levels, increased urine free cortisol, and high serum cortisol levels due to high serum levels of cortisol-binding globulin. Critically ill patients frequently have hypercortisolism, usually with suppression of serum ACTH. Depressed patients also have hypercortisolism that can be nearly impossible to distinguish biochemically from Cushing syndrome but without clinical signs of Cushing syndrome. Cushing syndrome can be misdiagnosed as anorexia nervosa (and vice versa) owing to the muscle wasting and extraordinarily high urine free cortisol levels found in anorexia. Patients with severe obesity frequently have an abnormal dexamethasone suppression test, but the urine free cortisol is usually normal, as is diurnal variation of serum cortisol. Patients with familial cortisol resistance have hyperandrogenism, hypertension, and hypercortisolism without actual Cushing syndrome. Excessive ingestion of gamma-hydroxybutyric acid (GHB, sodium oxybate) can also induce ACTH-dependent Cushing syndrome that resolves after the drug is stopped.

Some adolescents develop violaceous striae on the abdomen, back, and breasts; these are known as “striae distensae” and are not indicative of Cushing syndrome. Patients receiving antiretroviral therapy for HIV-1 infection frequently develop partial lipodystrophy with thin extremities and central obesity with a dorsocervical fat pad (“buffalo hump”) causing pseudo-Cushing syndrome.

► Treatment

Patients must receive treatment for cortisol-dependent comorbidities, including osteoporosis, psychiatric disorders, diabetes mellitus, hypertension, hypokalemia, muscle weakness, and infections. Bone densitometry is recommended for all patients and treatment is commenced for patients with osteoporosis.

A. Surgical Therapy

Pituitary Cushing disease is best treated with transsphenoidal selective resection of the pituitary adenoma, even when the pituitary MRI is normal or inconclusive. With an experienced pituitary neurosurgeon, remission rates range

from 80% to 90%. Postoperative hyponatremia occurs frequently; serum sodium should be monitored often for the first 2 weeks postoperatively. The patient should be screened for secondary hypothyroidism with a serum free T₄ within 1–2 weeks after surgery. After successful pituitary surgery, the rest of the pituitary usually returns to normal function; however, the pituitary corticotrophs remain suppressed and require 6–36 months to recover normal function. Therefore, patients receive empiric replacement-dose hydrocortisone postoperatively. Postoperative secondary adrenal insufficiency is a mark of successful pituitary surgery; screening may include a morning serum cortisol 8 hours following the prior evening dose of hydrocortisone. The cosyntropin test becomes abnormal by 2 weeks following successful pituitary surgery. Patients with secondary adrenal insufficiency and their families require patient education about the condition and must continue corticosteroid replacement until a cosyntropin stimulation test is normal. A pituitary MRI is obtained about 3 months postoperatively and repeated as indicated for clinical evidence of recurrent Cushing disease or Nelson syndrome, the progressive enlargement of ACTH-secreting pituitary tumors following bilateral adrenalectomy.

Cushing disease may persist after pituitary surgery, particularly when there has been cavernous sinus involvement. After apparent successful pituitary surgery, Cushing disease recurs in 16% after a mean of 38 months. Patients must have repeated evaluations for recurrent Cushing disease for years postoperatively. For patients with persistent or recurrent Cushing disease, repeat transsphenoidal pituitary surgery may be warranted if the recurrent tumor is visible and deemed resectable. Otherwise, bilateral laparoscopic adrenalectomy is usually the best treatment option, particularly for patients with very severe disease, since it renders an immediate remission in a condition with significant morbidity and mortality. Residual or recurrent ACTH-secreting pituitary tumors may also be treated with stereotactic radiosurgery, which normalizes urine free cortisol in 70% of patients within a mean of 17 months, compared with a 23% remission rate with conventional radiation therapy. Pituitary radiosurgery can also be used to treat Nelson syndrome.

Ectopic ACTH-secreting tumors should be surgically resected. If the tumor cannot be localized or is metastatic, laparoscopic bilateral adrenalectomy is usually recommended. Medical treatment with an oral combination of mitotane (3–5 g/24 h), ketoconazole (0.4–1.2 g/24 h), and metyrapone (3–4.5 g/24 h) often suppresses the hypercortisolism.

B. Medical Therapy

For patients with Cushing syndrome who decline surgery or for whom surgery has been unsuccessful, treatment with osilodrostat orally twice daily can normalize urine free cortisol and improve the manifestations of hypercortisolism. Mineralocorticoid hypertension can be treated with spironolactone, eplerenone, and dihydropyridine calcium channel blockers. Women with hyperandrogenism may be treated with flutamide. Cabergoline, 0.5–3.5 mg orally twice weekly, reduced hypercortisolemia in 40% of

patients with Cushing disease in one small study. Pasireotide, a multireceptor-targeting somatostatin analog, is a treatment option for refractory ACTH-secreting pituitary tumors causing Cushing disease or Nelson syndrome. Ketoconazole inhibits adrenal steroidogenesis and is another treatment option when given in doses of about 200 mg orally every 6 hours; however, it is marginally effective and can cause liver toxicity. Metyrapone can suppress hypercortisolism; required median oral daily doses are 1250–1500 mg/day in divided doses. It may be combined with ketoconazole. Metyrapone also may be used for patients with secretory adrenocortical carcinoma whose hypercortisolism is not fully controlled with mitotane.

Metastatic ACTH-producing tumors that are visible with Octreoscan or ⁶⁸Ga-DOTATATE-PET imaging have somatostatin receptors. Such tumors may respond to therapy with somatostatin analogs; pasireotide LAR (60 mg intramuscularly every 28 days) or octreotide LAR (30–40 mg intramuscularly every 28 days) slows progression of the malignancy and reduces ACTH secretion in up to half such patients. Potassium-sparing diuretics are often helpful. Radionuclide therapy with several cycles of ¹⁷⁷Lu-DOTATATE has produced remissions in some patients.

Patients who are successfully surgically treated for Cushing syndrome typically develop “cortisol withdrawal syndrome,” even when given replacement corticosteroids for adrenal insufficiency. Manifestations can include hypotension, nausea, fatigue, arthralgias, myalgias, pruritus, and flaking skin. Increasing the hydrocortisone replacement to 30 mg orally twice daily can improve these symptoms; the dosage is then reduced slowly as tolerated.

Benign adrenal adenomas may be resected laparoscopically if they are smaller than 6 cm; cure is achieved in most patients. However, most patients experience prolonged secondary adrenal insufficiency. Patients with bilateral adrenal macronodular hyperplasia usually require bilateral adrenalectomies and an evaluation for Carney complex that can be confirmed with a genetic evaluation for activating mutations in the gene PRKAR1A or genetic changes at chromosome 2p16.

Adrenocortical carcinomas are resected surgically. If the adrenocortical carcinoma was functional, postoperative secondary adrenal insufficiency is a good prognostic sign, with an increased chance that the tumor was completely resected without metastases; however, detectable postoperative cortisol levels predict metastases, even if no metastases are detectable on scans.

Patients with secretory adrenocortical carcinomas are usually treated with mitotane postoperatively, particularly if metastases are visible or cortisol is detectable postoperatively. Patients with nonsecretory metastatic adrenocortical carcinomas have also responded to mitotane. Mitotane is typically given for 2–5 years postoperatively. It is given orally with meals, beginning with 0.5 g twice daily, increasing to 1 g twice daily within 2 weeks, with subsequent increased doses every 2–3 weeks to reach serum levels of 14–20 mcg/mL. Unfortunately, only half the patients are able to reach these levels due to side effects. Mitotane can cause hypogonadism, can suppress TSH and cause hypothyroidism, and can cause primary adrenal insufficiency.

Replacement hydrocortisone or prednisone should be started when mitotane doses reach 2 g daily. The replacement dose of oral hydrocortisone starts at 15 mg in the morning and 10 mg in the afternoon but must often be doubled or tripled because mitotane increases cortisol metabolism and cortisol-binding globulin levels; the latter can artifactually raise serum cortisol levels. Combined chemotherapy with etoposide, doxorubicin, cisplatin, and mitotane (EDP-M) appears to be the most effective regimen for recurrent or metastatic adrenocortical carcinoma.

Osilodrostat is an oral drug that reduces cortisol synthesis by blocking the adrenal enzyme 11B-hydroxylase. Side effects include adrenal insufficiency as well as hirsutism and acne, caused by increased adrenal testosterone production. ACTH-secreting pituitary tumors may enlarge with long-term therapy.

► Prognosis

The manifestations of Cushing syndrome regress with time, but patients may have residual cognitive or psychiatric impairment, muscle weakness, osteoporosis, and sequelae from vertebral fractures. Continued impaired quality of life is more common in women compared to men. Younger patients have a better chance for full recovery.

Patients with Cushing syndrome from a benign adrenal adenoma experience a 5-year survival of 95% and a 10-year survival of 90%, following a successful adrenalectomy. Patients with Cushing disease from a pituitary adenoma experience a similar survival if their pituitary surgery is successful, which can be predicted if the postoperative nonsuppressed serum cortisol is less than 2 mcg/dL (55 nmol/L). Following successful treatment, overall mortality remains particularly higher for patients with older age at diagnosis, higher preoperative ACTH concentrations, and longer duration of hypercortisolism. Patients in remission from Cushing disease continue to experience a higher mortality rate than expected, particularly from ischemic heart disease and from cerebral infarction, bacterial infections, and suicide.

Patients who have a complete remission after transphenoidal surgery have about a 15–20% chance of recurrence over the next 10 years. Patients with failed pituitary surgery may require pituitary radiation therapy, which has its own morbidity. Laparoscopic bilateral adrenalectomy may be required. Recurrence of hypercortisolism may occur as a result of growth of an adrenal remnant stimulated by high levels of ACTH. The prognosis for patients with ectopic ACTH-producing tumors depends on the aggressiveness and stage of the particular tumor. Patients with ACTH of unknown source have a 5-year survival rate of 65% and a 10-year survival rate of 55%.

In patients with adrenocortical carcinoma, 5-year survival rates of treated patients have correlated with the ENSAT stage. For stage 1, the 5-year survival was 81%; for stage 2, 61%; for stage 3, 50%; and for stage 4, 13%. Improved survival has been associated with younger age, resection of the primary tumor, stage at diagnosis, adjuvant radiation to the tumor bed after resection, and adjuvant therapy with mitotane.

► Complications

Following bilateral adrenalectomy for Cushing disease, a pituitary adenoma may enlarge progressively (Nelson syndrome), causing local destruction (eg, visual field impairment, cranial nerve palsy) and hyperpigmentation. Following successful therapy for Cushing syndrome, secondary adrenal insufficiency occurs and requires long-term corticosteroid replacement. Five years after successful surgery, secondary hypoadrenalinism resolves in about 58% of patients with pituitary Cushing disease, 82% of those with ectopic ACTH, and only 38% of those who had an adrenal tumor.

► When to Refer

Dexamethasone suppression test is abnormal.

► When to Admit

- Transsphenoidal hypophysectomy.
- Adrenalectomy.
- Resection of ectopic ACTH-secreting tumor.

Babot M et al. Cushing's syndrome: Overview of clinical presentation, diagnostic tools and complications. Best Pract Res Clin Endocrinol Metab. 2020;34:101380. [PMID: 32165101]

Gami BP et al. Accuracy of laboratory tests for the diagnosis of Cushing syndrome. J Clin Endocrinol Metab. 2020;105:2081. [PMID: 32133504]

Pivonello R et al. Efficacy and safety of osilodrostat in patients with Cushing's disease (LINC 3): a multicentre phase III study with a double-blind, randomised withdrawal phase. Lancet Diabetes Endocrinol. 2020;8:748. [PMID: 32730798]

Ragnarsson O. Cushing's syndrome: Disease monitoring, recurrence, surveillance with biomarkers or imaging studies. Best Pract Res Clin Endocrinol Metab. 2020;34:101382. [PMID: 32139169]

PRIMARY ALDOSTERONISM

ESSENTIALS OF DIAGNOSIS

- Hypertension may be severe or drug-resistant.
- Hypokalemia (in minority of patients) may cause polyuria, polydipsia, muscle weakness.
- Low plasma renin; elevated plasma and urine aldosterone levels.

► General Considerations

Primary aldosteronism (hyperaldosteronism) refers to renin-independent, inappropriately high and nonsuppressible aldosterone secretion and is associated with adverse cardiovascular disorders. Although most affected patients have hypertension, some may be normotensive. The prevalence of primary aldosteronism in patients with suppressed PRA is 11% in normotensive individuals, 17% in those with stage 1 untreated hypertension, 25% in those with

stage 2 untreated hypertension, and 51% in those with treatment-resistant hypertension. It should be suspected with early-onset hypertension or stroke before age 50 years. It may be difficult to distinguish primary aldosteronism from cases of low renin essential hypertension, with which it may overlap. Patients of all ages may be affected, but the peak incidence is between 30 years and 60 years. Excessive aldosterone production increases sodium retention and suppresses plasma renin. It increases renal potassium excretion, which can lead to hypokalemia. Cardiovascular events are more prevalent in patients with aldosteronism (35%) than in those with essential hypertension (11%).

Primary aldosteronism is most frequently caused by bilateral adrenal cortical hyperplasia (75%) that is more common in men with a 4:1 ratio, peaking between ages 50 and 60. Primary aldosteronism may be also caused by a unilateral aldosterone-producing adrenal cortical adenoma (Conn syndrome, 25%) that is more common in women with a 2:1 ratio, peaking between ages 30 and 50. It is important to distinguish the two, since a unilateral aldosteronoma (Conn syndrome) may be cured by surgical resection, whereas patients with bilateral adrenal hyperplasia are treated medically.



Clinical Findings

A. Symptoms and Signs

Primary aldosteronism is the most common cause of refractory hypertension in youths and middle-aged adults. Patients have hypertension that is typically moderate but may be severe. Some patients have only diastolic hypertension, without other symptoms and signs. Edema is rarely seen in primary aldosteronism. Hypokalemia can produce muscle weakness, paresthesias with tetany, headache, polyuria, and polydipsia.

B. Laboratory Findings

Plasma potassium should be determined in hypertensive individuals. However, **hypokalemia, once thought to be the hallmark of hyperaldosteronism, is present in only 37% of affected patients;** 50% of those with an aldosterone-producing adenoma and 17% of those with adrenal hyperplasia. An elevated serum bicarbonate (HCO_3) concentration indicates metabolic alkalosis and is commonly present.

Testing for primary aldosteronism should be considered for all hypertensive patients with any of the following: (1) sustained hypertension above 150/100 mm Hg on 3 different days; (2) hypertension resistant to three conventional antihypertensive drugs, including a diuretic; (3) controlled blood pressure requiring four or more antihypertensive drugs; (4) hypokalemia, particularly when unrelated to diuretics; (5) personal or family history of early-onset hypertension or cerebrovascular accident at age 40 or younger; (6) first-degree relative with primary aldosteronism; (7) presence of an adrenal mass; and (8) low PRA.

For at least 2 weeks prior to testing, patients should have any hypokalemia corrected and then consume a diet high in NaCl (more than 6 g/day) and ideally withhold certain medications: all diuretics, ACE inhibitors, and ARBs (stimulate PRA); and beta-blockers, clonidine, and NSAIDs (suppress PRA); oral estrogens and oral contraceptives should also ideally be held. Medications that are allowed include extended-release verapamil, hydralazine, terazosin, and doxazosin.

For blood testing, the patient should be out of bed for at least 2 hours and seated for 15–60 minutes before the blood draw, which should preferably be obtained between 8 AM and 10 AM. The blood should be drawn slowly with a syringe and needle (rather than a vacutainer) at least 5 seconds after tourniquet release and without fist clenching. Plasma potassium, rather than the routine serum potassium, should be measured in cases of unexpected hyperkalemia. Plasma potassium levels must be normal, since hypokalemia suppresses aldosterone. For practical purposes, the same blood draw can be used for simultaneous assays for plasma potassium, serum aldosterone, and PRA. Patients with primary aldosteronism have a suppressed PRA below or near 1.0 ng/mL/h. Suppressed PRA with a serum aldosterone concentration greater than 15 ng/dL (420 pmol/L) indicates probable primary hyperaldosteronism. Serum aldosterone (ng/dL) to PRA (ng/mL/h) ratios less than 24 exclude primary aldosteronism; ratios between 24 and 30 are indeterminate; ratios between 30 and 64 are suspicious; a ratio above 64 helps confirm the diagnosis of primary aldosteronism. To help confirm the diagnosis of aldosteronism, especially for patients with a suppressed PRA but lower serum aldosterone levels, a 24-hour urine is collected in an acidified container for aldosterone, cortisol, and creatinine; **urine aldosterone greater than 12 mcg/24 h (33 nmol/24 h)** confirms primary aldosteronism with 93% specificity.

Genetic testing is recommended for patients with confirmed primary aldosteronism by age 20 years and those with a family history of primary aldosteronism or stroke at young age (under age 40). The testing is for familial corticosteroid remediable aldosteronism.

C. Imaging

Some patients with undiagnosed primary aldosteronism are incidentally found to have an adrenal nodule (incidentaloma) during abdominal or chest imaging. All patients with biochemically confirmed primary aldosteronism require a thin-section CT scan of the adrenals to screen for a rare adrenal carcinoma. In the absence of a large adrenal carcinoma, adrenal CT scanning cannot reliably distinguish unilateral from bilateral aldosterone excess, having both a sensitivity and specificity of 78% for unilateral aldosteronism. Therefore, the decision to perform a unilateral adrenalectomy should not be based solely on the adrenal CT scan. Adrenal vein sampling is often required.

D. Adrenal Vein Sampling

Unfortunately, bilateral selective adrenal vein sampling is invasive, expensive and not widely available. Adrenal vein sampling has a sensitivity of 95% and a specificity of 100% but only when performed by an experienced radiologist. This procedure entails a 0.6% risk of major complications.

The procedure (and surgery) may not be required for patients whose blood pressure is well controlled with spironolactone or eplerenone and for those with familial hyperaldosteronism. It is indicated only if surgery is contemplated in order to direct the surgeon to the correct adrenal gland. In such cases, adrenal vein sampling can be useful to identify the adrenal to be removed when there is no visible adrenal adenoma on CT imaging. Adrenal vein sampling can also help avoid mistaken removal of an incidental nonsecreting adrenal adenoma. Adrenal vein sampling is not required in patients who have a classic adrenal adenoma (Conn syndrome), which is characterized by spontaneous hypokalemia and a unilateral adrenal adenoma 10 mm or larger on CT.

Before this procedure, the patient must be properly prepared (see Laboratory Findings). However, patients with a persistently suppressed PRA may continue mineralocorticoid blockade. Lateralization is present when the aldosterone:cortisol ratio from one adrenal vein is at least four times that from the opposite adrenal vein.

Aldosterone hypersecretion that is lateralized to one adrenal usually indicates that adrenal has a unilateral aldosteronoma or hyperplasia, particularly when aldosterone secretion from the contralateral adrenal is suppressed.

Differential Diagnosis

The differential diagnosis of primary aldosteronism includes other causes of hypokalemia in patients with essential hypertension, especially diuretic therapy; chronic depletion of intravascular volume stimulates renin secretion and secondary hyperaldosteronism (see Table 21–3).

Apparent mineralocorticoid excess syndrome may be caused by real (black) licorice (derived from anise) or anise-flavored drinks (sambuca, pastis), which contain glycyrrhetic acid. Abiraterone, a drug therapy for prostate cancer, causes hypertension and hypokalemia. Similarly, posaconazole, an oral antifungal drug, can cause pseudohyperaldosteronism with hypertension and hypokalemia.

Oral contraceptives may increase aldosterone secretion in some patients. Renal vascular disease can cause severe hypertension with hypokalemia but PRA is high. Excessive adrenal secretion of other corticosteroids (besides aldosterone), certain congenital adrenal enzyme disorders, and primary cortisol resistance may also cause hypertension with hypokalemia. The differential diagnosis also includes Liddle syndrome, an autosomal dominant cause of hypertension and hypokalemia resulting from excessive sodium absorption from the renal tubule; renin and aldosterone levels are low.

Complications

Cardiovascular complications occur more frequently in primary aldosteronism than in idiopathic hypertension. Following unilateral adrenalectomy for Conn syndrome, suppression of the contralateral adrenal may result in temporary postoperative hypoaldosteronism, characterized by hyperkalemia and hypotension.

Treatment

The **unilateral adrenal adenoma** of Conn syndrome is usually treated by laparoscopic adrenalectomy. During pregnancy, such surgery is best performed during the second trimester. However, long-term medical therapy is an option for unilateral hyperaldosteronism, if adequate blood pressure control can be maintained.

Bilateral adrenal hyperplasia is best treated with medical therapy. Medical treatment must include a potassium-sparing diuretic, particularly spironolactone, eplerenone, or amiloride. Spironolactone is the most effective drug but also has antiandrogen activity and men frequently experience breast tenderness, gynecomastia, or reduced libido; initial dose is 12.5–25 mg orally once daily and may be titrated to 200 mg daily. Spironolactone might lead to undervirilization of male infants and is contraindicated in pregnancy; reproductive-age women are cautioned to use contraception during therapy. Eplerenone, 25–50 mg orally twice daily, is favored during pregnancy (FDA pregnancy category B) and for men, since it does not have antiandrogen effects. Blood pressure must be monitored daily when beginning these anti-mineralocorticoid medications; significant drops in blood pressure have occurred when these drugs are added to other antihypertensives. Other antihypertensive drugs may be required, particularly amlodipine, and ACE inhibitors or ARBs. Corticosteroid-remediable aldosteronism is very rare, but may respond well to suppression with low-dose corticosteroids.

Prognosis

The hypertension from unilateral adrenal adenoma is reversible in about two-thirds of cases but persists or returns despite surgery in the remainder. The prognosis is much improved by early diagnosis and treatment. Only 2% of aldosterone-secreting adrenal tumors are malignant.

Gershuni VM et al. Clinical presentation and surgical outcomes in primary aldosteronism differ by race. *J Surg Oncol.* 2020; 121:456. [PMID: 31858609]

Hundemer GL et al. Management of endocrine disease: the role of surgical adrenalectomy in primary aldosteronism. *Eur J Endocrinol* 2020;183:R185. [PMID: 33077688]

Pillai P et al. Primary aldosteronism: cardiovascular risk, diagnosis, and management. *Cardiol Rev.* 2020;28:84. [PMID: 31868768]

Williams TA et al. Management of endocrine disease: diagnosis and management of primary aldosteronism: the Endocrine Society guideline 2016 revisited. *Eur J Endocrinol.* 2018;179: R19. [PMID: 29674485]

PHEOCHROMOCYTOMA & PARAGANGLIOMA



ESSENTIALS OF DIAGNOSIS

- ▶ “Attacks” of headache, perspiration, palpitations, anxiety. Multisystem crisis.
- ▶ Hypertension: sustained but often paroxysmal, especially during surgery or delivery; may be orthostatic.
- ▶ Elevated plasma free fractionated metanephrenes. Normal serum T₄ and TSH.
- ▶ Tumoral secretion of norepinephrine or neuropeptide Y cause hypertension.
- ▶ Excessive epinephrine causes tachyarrhythmias.

► General Considerations

Both pheochromocytomas and non-head-neck paragangliomas are rare tumors of the sympathetic nervous system. Pheochromocytomas arise from the adrenal medulla and usually secrete both epinephrine and norepinephrine. Paragangliomas (“extra-adrenal pheochromocytomas”) arise from sympathetic paranglia and often metastasize. About 50% of paragangliomas secrete norepinephrine; the rest are nonfunctional or secrete only dopamine, normetanephrine, or chromogranin A (CgA). These tumors may be located in either or both adrenals or anywhere along the sympathetic nervous chain, and sometimes in the mediastinum, heart, or bladder.

These tumors are particularly dangerous and deceptive and cause death in at least one-third of patients prior to diagnosis. They account for less than 0.4% of hypertension cases. The incidence is higher in children and patients with moderate to severe hypertension, particularly in the presence of suspicious symptoms of headache, significant palpitations, or diaphoretic episodes. Nearly 50% of cases are discovered incidentally on imaging studies. They account for about 4% of adrenal incidentalomas. The yearly incidence is about 6 new cases per million. However, many cases are undiagnosed during life, since the prevalence of pheochromocytomas and paragangliomas in autopsy series is 1 in 2000.

Nonsecretory paragangliomas arise in the head or neck, particularly in the carotid body, jugular-tympanic region, or vagal body; only about 4% secrete catecholamines.

About 40% of patients with pheochromocytomas or paragangliomas harbor a germline mutation in 1 of at least 16 known susceptibility genes that predispose to the tumor, usually in an autosomal dominant manner with incomplete penetrance. Thorough genetic testing is recommended for all patients with these tumors.

von Hippel-Lindau (VHL) disease type 2 is associated with a 30% lifetime incidence of pheochromocytoma that can present as early as age 5 years or later in adulthood. Pheochromocytomas are usually adrenal, less likely to be malignant (3.5%), and more likely to be bilateral. About

25% of these patients are asymptomatic and normotensive at diagnosis. The condition is also associated with hemangiomas of the retina, cerebellum, brainstem, and spinal cord; hyperparathyroidism; pancreatic cysts; endolymphatic sac tumors; cystadenomas of the adnexa or epididymis; pancreatic neuroendocrine tumors; and renal cysts, adenomas, and carcinomas; inheritance is autosomal dominant.

MEN 2 (MEN 2A) is associated with medullary thyroid carcinoma, pheochromocytomas, hyperparathyroidism, and cutaneous lichen amyloidosis. Pheochromocytomas are often silent in MEN 2; at diagnosis, only about 50% have symptoms and fewer are hypertensive. The lack of symptoms may be due to earlier diagnosis through yearly screening of mutation carriers. **MEN 3 (MEN 2B)** may be familial, but usually arises from a *de novo* *ret* mutation; MEN 3 is associated with pheochromocytoma (50%), aggressive medullary thyroid carcinoma, mucosal neuromas, and Marfan-like habitus.

von Recklinghausen neurofibromatosis type 1 (NF-1) is associated with an increased risk of pheochromocytomas/paragangliomas as well as cutaneous neurofibromas, optic and brainstem gliomas, astrocytomas, vascular anomalies, hamartomas, malignant nerve sheath tumors, and smooth-bordered café au lait spots.

► Clinical Findings

A. Symptoms and Signs

Clinical manifestations of pheochromocytoma and paraganglioma depend on the manner in which the tumor is discovered. Pheochromocytomas may be relatively asymptomatic when they are diagnosed preemptively by screening members of kindreds harboring germline mutations that predispose to these tumors. Similarly, patients with pheochromocytomas discovered incidentally on CT scanning may have few symptoms. However, other pheochromocytomas can be lethal unless they are diagnosed and treated appropriately. Catastrophic hypertensive crisis and fatal cardiac arrhythmias can occur spontaneously or may be triggered by needle biopsy or manipulation of the mass, glucagon injection, vaginal delivery, trauma, anesthesia, or surgery (both unrelated to the tumor or for its removal). Exercise, bending, lifting, or emotional stress can trigger paroxysms. Bladder paragangliomas may present with paroxysms during micturition. Certain drugs can precipitate attacks: decongestants, amphetamines, cocaine, epinephrine, corticosteroids, fluoxetine and other selective serotonin reuptake inhibitors (SSRIs), metoclopramide, monoamine oxidase (MAO) inhibitors, caffeine, nicotine, and ionic intravenous contrast.

Clinical manifestations of pheochromocytoma typically include hypertension (81%) that may be paroxysmal or sustained, headache (60%), palpitations (60%), or diaphoresis (52%). About 58% of patients have episodic nonspecific “spells.” Other symptoms include anxiety (often with a sense of impending doom), weakness/fatigue, dyspnea, nausea/vomiting, tremor, dizziness, chest pain, abdominal pain, paresthesias, or constipation. Vasospasm during an attack can cause Raynaud syndrome, mottled cyanosis, or

facial pallor. As the attack subsides, facial flushing and drenching sweats can occur. Epinephrine secretion by an adrenal pheochromocytoma can cause episodic tachyarrhythmias and sometimes orthostatic hypotension or even syncope. Cardiac manifestations include acute coronary syndrome, cardiomyopathy, heart failure, and potentially fatal dysrhythmias. Catecholamine-induced cardiomyopathy can present with shock. Confusion, psychosis, paresthesias, seizures, transient ischemic attacks, or stroke may occur with cerebrovascular vasoconstriction or hemorrhagic stroke. Aneurysms may dissect. Abdominal pain, nausea, vomiting, and even ischemic bowel can occur. Patients may experience increased appetite, loss of weight, numbness, or fevers. During pregnancy, pheochromocytomas can produce hypertension and proteinuria, mimicking eclampsia; vaginal delivery can produce hypertensive crisis followed by postpartum shock. Painful bony metastases may be a presenting symptom of metastatic pheochromocytoma. A minority of patients are normotensive and asymptomatic, particularly when the tumor is nonsecretory or discovered at an early stage.

Pheochromocytomas can also rarely produce other “ectopic” peptide hormones, resulting in Cushing syndrome (ACTH), Verner-Morrison syndrome (VIP), or hypercalcemia (PTHrP). **Multisystem crisis** can occur, with manifestations of severe hypertension or hypotension, acute respiratory distress syndrome (ARDS), cardiomyopathy with acute heart failure, kidney dysfunction, liver failure, and death. Multisystem crisis can occur spontaneously, or it may be provoked by surgery, vaginal delivery, or treatment of metastatic disease.

B. Laboratory Findings

Pheochromocytomas are rare tumors, but they are deadly, and a missed diagnosis can be catastrophic. However, less than 1% of biochemical evaluations in patients with suspicious symptoms lead to a diagnosis of pheochromocytoma. More commonly, testing yields misleading minor elevations in tumor markers, particularly when levels are less than three times the upper limit of normal.

Plasma fractionated free metanephrenes is the most sensitive test for secretory pheochromocytomas and paragangliomas. Plasma levels of free metanephrenes are lower when the patient is supine than when ambulatory. For practicality, the blood specimen is usually obtained after the patient sits quietly in the laboratory for at least 15 minutes. The test is 97% sensitive for secretory tumors, so normal levels rule out secretory pheochromocytoma and paraganglioma with some certainty. The exceptions are patients who are being monitored because they harbor a germline mutation for familial pheochromocytoma; such patients with a pheochromocytoma are often asymptomatic early on and frequently have normal testing or only mild elevations in plasma metanephrenes. However, for other patients with severe hypertension or “spells” caused by a pheochromocytoma, plasma fractionated free metanephrenes are ordinarily at least three times the upper limit of normal. Such testing has a false-positive rate of 17%, usually with less dramatic elevations in plasma metanephrenes. False-positive test results should be

particularly suspected when the ratio of normetanephrine to norepinephrine is less than 0.52 or the ratio of metanephrenine to epinephrine is less than 4.2. In such cases, it is best to repeat biochemical testing under optimal conditions, eg, after eliminating potentially recovery from illness, treating sleep apnea, or eliminating potentially interfering drugs. Such drugs (including tricyclic antidepressants, antipsychotics, levodopa, MAO inhibitors, and antidepressants that are norepinephrine reuptake inhibitors) should ideally be discontinued for at least 2 weeks before retesting. Patients may be retested while lying supine in a quiet room for 30–90 minutes before the blood is drawn. Most patients with marginal elevations in plasma fractionated free metanephrenes require confirmation with a 24-hour urine for fractionated metanephrenes and creatinine.

Urinary fractionated metanephrenes and creatinine effectively confirm most pheochromocytomas that were detected by elevated plasma fractionated free metanephrenes. A 24-hour urine specimen is obtained, although an overnight or shorter collection may be used; patients with pheochromocytomas generally have more than 2.2 mcg of total metanephrine per milligram of creatinine, and more than 135 mcg total catecholamines per gram creatinine. Urinary assay for total metanephrenes is about 97% sensitive for detecting functioning pheochromocytomas.

Plasma fractionated catecholamines may be helpful to confirm whether an adrenal tumor is a secretory pheochromocytoma. The test may also be useful for normotensive patients with a paraganglioma; the tumor may secrete only dopamine, which can be followed as a tumor marker.

Serum CgA is elevated in about 85% of patients with pheochromocytoma or paraganglioma and the levels correlate with tumor size, being higher in patients with metastatic disease. Serum CgA must be assayed in the fasting state, since levels rise after meals. Misleading elevated CgA levels also occur in patients with azotemia or hypergastrinemia, and in those treated with corticosteroids or proton pump inhibitors. Serum CgA is not specific for pheochromocytoma, so its measurement is not very useful for the initial diagnosis.

Clonidine suppression testing can help distinguish whether elevated plasma free normetanephrine levels are physiologic or indicative of pheochromocytoma. Plasma fractionated free metanephrenes are measured before the administration of clonidine (0.3 mg orally) and 3 hours afterward. A fall of plasma normetanephrine into the normal range or a fall of greater than 40% from baseline helps rule out the presence of a tumor.

Hyperglycemia is present in about 35% of patients but is usually mild. Proteinuria is present in about 10–20% of patients. Leukocytosis is common. Erythrocytosis or eosinophilia can occur. The ESR is sometimes elevated. PRA may be increased by catecholamines.

C. Imaging

1. CT and MRI scanning—When an adrenal pheochromocytoma is suspected, a *noncontrast* CT scan of the abdomen is performed, with thin sections through the adrenals. *Glucagon should not be used during scanning, since it can provoke hypertensive crisis in patients with a pheochromocytoma.*

MRI scanning has the advantage of not requiring intravenous contrast dye; its lack of radiation makes it the imaging of choice during pregnancy and for serial imaging. Both CT and MRI scanning have a sensitivity of about 90% for adrenal pheochromocytoma and a sensitivity of 95% for adrenal tumors over 0.5 cm. However, both CT and MRI are less sensitive for detecting recurrent tumors, metastases, and extra-adrenal paragangliomas. If no adrenal tumor is found, the scan is extended to include the entire abdomen, pelvis, and chest.

2. Nuclear imaging—⁶⁸Ga-DOTATOC-PET scanning is the most sensitive scan, detecting about 90% of pheochromocytomas, paragangliomas, and metastases. However, it is not entirely specific for these tumors. PET imaging gives crisper imaging than scintigraphy. Nuclear imaging is usually combined with volumetric imaging (CT or MRI) to determine the precise size and location of tumors.

¹⁸FDG-PET scanning detects about 54% of metastases but is more sensitive for patients with SDHB germline mutations. However, ¹⁸FDG-PET scanning is not specific for pheochromocytoma or paraganglioma.

¹²³I-MIBG whole-body scintigraphy can lateralize and confirm adrenal pheochromocytomas with a sensitivity of over 90%, but is only about 67% sensitive for extra-adrenal (paraganglioma) tumors and metastases and is also less sensitive for MEN 2- or MEN 3-related pheochromocytomas. ¹²³I-MIBG scintigraphy is also less sensitive for particularly aggressive tumors. Prior to the scan, the patient is given KI to competitively inhibit the uptake of free ¹²³I into the thyroid. Also, drugs that reduce ¹²³I-MIBG uptake should be avoided: tricyclic antidepressants and cyclobenzaprine (6 weeks); and amphetamines, decongestants, cocaine, phenothiazines, haloperidol, labetalol, and serotonin and norepinephrine reuptake inhibitors (2 weeks). Drug interference is suspected in negative ¹²³I-MIBG scans that do not show normal uptake in salivary glands.

Differential Diagnosis

Conditions that mimic pheochromocytoma include thyrotoxicosis, labile essential hypertension, myocarditis, glomerulonephritis or other renal lesions, eclampsia, acute intermittent porphyria, hypogonadal vascular instability (hot flushes), anxiety attacks, cocaine or amphetamine use, and clonidine withdrawal. Patients taking nonselective MAO inhibitor antidepressants can have hypertensive crisis after eating foods that contain tyramine. Patients with erythromelalgia can have hypertensive crises. Renal artery stenosis can cause severe hypertension and may coexist with pheochromocytoma. Plasma fractionated free metanephrenes can be elevated in sleep apnea or with stressful illness. On CT scan, adrenal pheochromocytomas must be distinguished from adrenal adenomas and other masses. ¹²³I-MIBG scintigraphy uptake in the adrenal glands can be physiologic uptake and can sometimes occur in benign adrenal adenomas.

Complications

All of the complications of severe hypertension may be encountered. In addition, a catecholamine-induced cardiomyopathy may develop. Severe heart failure and

cardiovascular collapse may develop in patients during a paroxysm. Sudden death may occur due to cardiac arrhythmia. ARDS and multisystem crisis can occur acutely and thus the initial manifestation of pheochromocytoma may be hypotension or even shock. Hypertensive crises with sudden blindness or cerebrovascular accidents are not uncommon.

After removal of the tumor, a state of severe hypotension and shock (resistant to epinephrine and norepinephrine) may ensue with precipitation of acute kidney injury or myocardial infarction. Hypotension and shock may occur from spontaneous infarction or hemorrhage of the tumor.

Pheochromocytomas and paragangliomas may metastasize. Cells can also be seeded within the peritoneum, either spontaneously or as a complication during surgical resection. Such seeding of the abdomen can lead to multifocal recurrent intra-abdominal tumors, a condition known as pheochromocytomatosis.

Medical Treatment

Patients must receive adequate treatment for hypertension and tachyarrhythmias prior to surgery for pheochromocytoma/paraganglioma. Patients are advised to measure their blood pressures daily and immediately during paroxysms. Some patients with pheochromocytoma or paraganglioma are not hypertensive and do not require preoperative antihypertensive management. Alpha-blockers or calcium channel blockers can be used, either alone or in combination. Blood pressure should be controlled before cardioselective beta-blockers are added for control of tachyarrhythmias. Normotensive patients with pheochromocytoma or sympathetic paraganglioma do not require preoperative alpha blockade, which increases their requirement for vasopressors and colloid after the tumor resection.

Alpha-blockers are typically administered in preparation for surgery. Phenoxybenzamine is a long-acting non-selective alpha-blocker with a half-life of 24 hours; it is given initially in a dosage of 10 mg orally every 12 hours, increasing gradually by about 10 mg/day about every 3 days until hypertension is controlled. Maintenance doses range from 10 mg/day to 120 mg/day. Doxazosin (half-life 22 hours), a selective alpha-1-blocker, may also be used in doses of 2–32 mg daily. Optimal alpha-blockade is achieved when supine arterial pressure is below 140/90 mm Hg or as low as possible for the patient to have a standing arterial pressure above 80/45 mm Hg.

Calcium channel blockers (nifedipine ER or nicardipine ER) are very effective and are usually added to alpha-blockers, but may be used alone. Nifedipine ER is initially given orally at a dose of 30 mg/day, increasing the dose gradually to a maximum of 60 mg twice daily. Calcium channel blockers are superior to phenoxybenzamine for long-term use, since they cause less fatigue, nasal congestion, and orthostatic hypotension. However, they should not be used for patients with severe heart failure. For acute hypertensive crisis (systolic blood pressure higher than 170 mm Hg), a nifedipine 10-mg capsule may be chewed and swallowed. Nifedipine is quite successful for treating acute hypertension in patients with pheochromocytoma/paraganglioma, even at home; it is reasonably safe as long as the blood pressure is carefully monitored.

Beta-blockers (eg, metoprolol XL) are often required after institution of alpha-blockade or calcium channel blockade. *The use of a beta-blocker as initial antihypertensive therapy has resulted in an “unopposed alpha” status that causes paradoxical worsening of hypertension.* Labetalol has combined alpha- and beta-blocking activity and is an effective agent, but can cause paradoxical hypertension if used as the initial antihypertensive agent. Labetalol can also interfere with catecholamine determinations in some laboratories and reduces the tumor's uptake of radioisotopes, such that it must be discontinued for at least 4–7 days before ¹²³I-MIBG or ¹⁸FDG-PET scanning or therapy with high-dose ¹³¹I-MIBG.

► Surgical Treatment

Surgical removal of pheochromocytomas or abdominal paragangliomas is the treatment of choice. For surgery, a team approach—endocrinologist, anesthesiologist, and surgeon—is critically important. Laparoscopic surgery is preferred, but large and invasive tumors require open laparotomy. Patients with small familial or bilateral pheochromocytomas may undergo selective resection of the tumors, sparing the adrenal cortex; however, there is a recurrence rate of 10% over 10 years.

Prior to surgery, blood pressure control should be maintained for a minimum of 4–7 days or until optimal cardiac status is established. It may take a week or even months to correct ECG changes in patients with catecholamine myocarditis, and it may be prudent to defer surgery until then in such cases. Patients must be very closely monitored during surgery to promptly detect sudden changes in blood pressure or cardiac arrhythmias.

Intraoperative severe hypertension is managed with continuous intravenous nicardipine, 2–6 mcg/kg/min, or nitroprusside, 0.5–10 mcg/kg/min. Prolonged nitroprusside administration can cause cyanide toxicity. Tachyarrhythmia is treated with intravenous atenolol (1 mg boluses), esmolol, or lidocaine.

Autotransfusion of 1–2 units of blood at 12 hours preoperatively plus generous intraoperative volume replacement reduces the risk of postresection hypotension and shock caused by desensitization of the vascular alpha-1-receptors. Shock is treated with intravenous saline or colloid and high doses of intravenous norepinephrine. Intravenous 5% dextrose is infused postoperatively to prevent hypoglycemia.

► Pheochromocytoma in Pregnancy

Although rare, pheochromocytoma must always be considered in women with hypertension or tachycardia who are planning pregnancy. Susceptible members of known kindreds with familial pheochromocytoma syndromes should be screened for pheochromocytoma *while planning* pregnancy, even if totally asymptomatic. During pregnancy, women with hypertension, heart failure, or pulmonary edema should be screened for pheochromocytoma. Fetal ultrasound may also detect pheochromocytoma as an incidental adrenal mass. Untreated pheochromocytoma results in mortality rates of 25% for the mother and 50% in the fetus. The diagnosis is typically delayed, since

hypertension, tachycardia, abdominal pain, and chest pains are often attributed to preeclampsia and pregnancy itself. A suspicion for pheochromocytoma is confirmed with elevated fasting plasma free fractionated metanephrenes drawn at rest. MRI is preferred over ultrasound to detect an adrenal mass. In diagnosed cases, the mother should have genetic testing for germline mutations associated with pheochromocytoma. Affected women with hypertension are treated with phenoxybenzamine, calcium channel blockade (nifedipine or nicardipine), or both. Beta-blockers should be used judiciously, since they can cause intrauterine growth retardation. The optimal time for laparoscopic surgical removal of a pheochromocytoma is during the second trimester and before 24 weeks' gestation. Women with a pheochromocytoma diagnosed after 28 weeks' gestation are best treated medically until they can have an elective cesarean section at 38 weeks' gestation.

► Metastatic Pheochromocytoma & Paraganglioma

Surgical histopathology for pheochromocytoma and paraganglioma cannot reliably determine whether a tumor is malignant. Only the presence of metastases defines malignancy, such that a WHO endocrine tumor classification uses the term “metastatic pheochromocytoma” to replace “malignant pheochromocytoma.” Therefore, all pheochromocytomas and paragangliomas must be approached as possibly malignant. It is essential to recheck blood pressure and plasma fractionated metanephrine levels about 4–6 weeks postoperatively, at least every 6 months for 5 years, then yearly for life and immediately if hypertension, suspicious symptoms, or metastases become evident.

Metastases from a pheochromocytoma or paraganglioma are visible in only about 35% when the primary tumor is discovered. The other 65% of metastases emerge clinically an average of 5.5 years (range 0.3–53 years) after the initial diagnosis. Since some metastases are indolent, it is important to tailor treatment to each individual according to their tumor's aggressiveness. Most surgeons resect the main tumor and larger metastases (debulking). Asymptomatic, indolent metastases may be kept under close surveillance without treatment.

A. Chemotherapy

The most common chemotherapy regimen combines intravenous cyclophosphamide, vincristine, and dacarbazine (Table 39–3). About one-third of patients experience some degree of temporary remission. Another chemotherapy regimen uses temozolomide, which is usually the best-tolerated chemotherapy and is particularly effective for metastatic pheochromocytoma or paraganglioma in patients with *SDHB* germline mutations. Sunitinib, a tyrosine kinase inhibitor, can also produce remissions. Metyrosine reduces catecholamine synthesis but does not slow the growth of metastases.

B. Targeted Radioisotope Therapy

1. **¹³¹I-MIBG**—About 60% of patients with metastatic pheochromocytoma or paraganglioma have tumors with

sufficient uptake of ^{123}I -MIBG on diagnostic scanning to allow for therapy with high-activity ^{131}I -MIBG. Azedra (^{131}I Idobenguanine) is FDA-approved for treating patients with metastatic pheochromocytoma or paraganglioma. Medications that reduce MIBG uptake must be avoided, particularly labetalol, phenothiazines, tricyclics, and sympathomimetics. Myelodysplastic syndrome and leukemia can develop several years after ^{131}I -MIBG therapy, with the risk proportional to the cumulative amount of isotope. ARDS and multisystem failure occur rarely after ^{131}I -MIBG therapy, particularly in patients with pretreatment proteinuria.

2. Peptide receptor radionuclide treatment (PRRT)—This therapy uses a radioisotope-tagged somatostatin analog against neuroendocrine tumors that express somatostatin receptors. ^{177}Lu -DOTATATE (Lutathera) is FDA-approved for treating patients with metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs); it is being used off-label and on protocol to treat patients with metastatic pheochromocytoma and paraganglioma tumors, 90% of which are avid for PRRT. The objective response rate is 25%, and the short-term disease control rate is 84%.

C. Treatment for Bone Metastases

Patients with significant osteolytic bone metastases may be treated with external beam radiation therapy. Patients with vertebral metastases and spinal cord compression require surgical decompression and kyphoplasty. Intravenous zoledronic acid or subcutaneous denosumab may also be administered to patients with osteolytic bone metastases.

▶ Prognosis

A pheochromocytoma or sympathetic paraganglioma is considered malignant if metastases are present, but metastases may take many years to become clinically evident. Therefore, lifetime surveillance is recommended. Malignancy is more likely for larger tumors and for paragangliomas. The prognosis is good for patients with pheochromocytomas that are resected before causing cardiovascular damage. Hypertension usually resolves after successful surgery, but may persist or return in 25% of patients despite successful surgery. In such cases, biochemical reevaluation is required to detect a possible second or metastatic pheochromocytoma.

The surgical mortality is under 3% with the use of laparoscopic surgical techniques, intraoperative monitoring, and preoperative blood pressure control with alpha-blockers or calcium channel blockers.

Patients with metastatic pheochromocytoma or paraganglioma have an extremely variable prognosis. Some metastases are indolent for several decades after the primary tumor diagnosis. Metastases from head-neck paragangliomas are particularly slow-growing. However, some of these tumors are extremely aggressive. Rapid disease progression has been associated with male sex, older age, larger primary tumor size, dopamine hypersecretion, failure to undergo primary tumor resection, very high tumor

burden, and metastases that are visible at the time of primary tumor diagnosis.

- Groeben H et al. International multicentre review of perioperative management and outcome for catecholamine producing tumours. *Br J Surg*. 2020;107:e170. [PMID: 31903598]
- Jasim S et al. Metastatic pheochromocytoma and paraganglioma: management of endocrine manifestations, surgery and ablative procedures, and systemic therapies. *Best Pract Res Clin Endocrinol Metab*. 2020;34:101354. [PMID: 31685417]
- Neumann HPH et al. Pheochromocytoma and paraganglioma. *N Engl J Med*. 2019;38:552. [PMID: 31390501]
- Sbardella E et al. Pheochromocytoma: an approach to diagnosis. *Best Pract Res Clin Endocrinol Metab*. 2020;34:101346. [PMID: 31708376]

INCIDENTALLY DISCOVERED ADRENAL MASSES

Adrenal incidentalomas are defined as adrenal nodules that are discovered incidentally on up to 4% of abdominal CT or MRI scans obtained for other reasons. Although the overwhelming majority of adrenal incidentalomas are benign adrenal adenomas, it is always necessary to determine whether such masses are malignant or pheochromocytomas and whether they secrete excessive cortisol or aldosterone. Patients with an adrenal nodule and any possible manifestation of hypercortisolism should be screened for Cushing syndrome with a plasma ACTH, serum cortisol, and serum DHEAS; patients with a low or low-normal ACTH, a suppressed DHEAS, or a high cortisol should then be assessed with a 1-mg dexamethasone suppression test (see Cushing syndrome). Patients with hypertension are screened for primary aldosteronism with a PRA and serum aldosterone (see Primary Aldosteronism). Adrenal incidentalomas should be assessed for pheochromocytoma if their unenhanced CT density is greater than or equal to 10 HU, particularly when their CT diameter exceeds 3 cm, and in patients with hypertension or suspicious symptoms; screening is done with plasma fractionated free metanephrenes.

When an adrenal incidentaloma larger than 4 cm is detected in a patient without a history of malignancy, it should be resected, unless it is an unmistakably benign myelolipoma, hemorrhage, or adrenal cyst. Masses 3–4 cm may be resected if they have suspicious features (heterogeneity or irregularity). Smaller adrenal incidentalomas are usually observed after endocrine testing. A *noncontrast* CT scan should be performed to determine the density of the mass. About 99.5% of adrenal pheochromocytomas have a density greater than or equal to 10 HU; patients with adrenal incidentalomas with densities greater than or equal to 10 HU that are not resected require both clinical follow-up and CT follow-up in 6–12 months.

- Bourdeau I et al. Management of endocrine disease: differential diagnosis, investigation and therapy of bilateral adrenal incidentalomas. *Eur J Endocrinol*. 2018;179:R57. [PMID: 29748231]
- Jason DS et al. Evaluation of an adrenal incidentaloma. *Surg Clin North Am*. 2019;99:721. [PMID: 31255202]

GASTROENTEROPANCREATIC NEUROENDOCRINE TUMORS (GEP-NETS) & CARCINOID TUMORS



ESSENTIALS OF DIAGNOSIS

- ▶ GEP-NETs are neuroendocrine tumors that originate in the gastrointestinal tract.
- ▶ About 60% of GEP-NETs are nonsecretory or secretory without clinical manifestations; they may be detected incidentally or may present with weight loss, abdominal pain, or jaundice.
- ▶ Carcinoid tumors arise from the intestines or lung, secrete serotonin, and may metastasize.

General Considerations

GEP-NETs are neuroendocrine tumors (NETs) that arise from the stomach, intestines, or endocrine pancreas.

The reported incidence of GEP-NETs has increased to about 37 per million yearly in the United States due to the incidental detection of small tumors on abdominal scans. About 40% are functional, producing hormones that also serve as tumor markers, important for diagnosis and follow-up. At presentation, 65% of GEP-NETs are unresectable or metastatic. Up to 25% of GEP-NETs are associated with one of four different inherited disorders: MEN 1, von Hippel-Lindau disease (VHL), neurofibromatosis 1 (NF-1), and tuberous sclerosis complex (TSC). In MEN 1, GEP-NETs are usually gastrinomas, carcinoids, or nonfunctioning tumors and are a common cause of death. In VHL, GEP-NETs are usually benign and multiple.

Insulinomas are the most common functional type of GEP-NET and are usually small, intrapancreatic, and benign (90%). Insulinomas are solitary in 95% of sporadic cases but are multiple in about 90% of cases arising in MEN 1. (See Chapter 27.)

Gastrinomas are often malignant (about 50%) and metastasize to the liver. Gastrinomas are typically found in the duodenum (49%), pancreas (24%), or lymph nodes (11%). Sporadic gastrinoma is rarely suspected at the onset of symptoms; typically, there is a 5-year delay in diagnosis. About 22% of gastrinomas arise in patients with MEN 1, who usually present at a younger age, often with multiple tumors; hyperparathyroidism can occur many years before or after the discovery of a gastrinoma.

Glucagonomas are rare and usually malignant, despite their benign histologic appearance. They usually arise as a large intrapancreatic tumor with 60% having liver metastases apparent by the time of diagnosis. Besides glucagon, they usually secrete additional hormones, including gastrin.

Somatostatinomas are very rare and usually single. They arise in the pancreas (50%) or small intestine. They secrete somatostatin.

VIPomas are quite rare and usually single intrapancreatic tumors with metastases usually evident (80%) at diagnosis. They produce vasoactive intestinal polypeptide (VIP).

Cholecystokinin-producing tumors (CCKomas) are rare tumors of the endocrine pancreas.

Carcinoid tumors can arise from the small bowel (53%, particularly terminal ileum), colon (12%), esophagus through duodenum (6%), or lung (bronchial carcinoid [5%]). About 20% of cases present with metastases without a known primary location. Carcinoids are multiple in about 28% of cases. Although tumors are usually indolent, metastases are common, particularly to liver, lymph nodes, and peritoneum.

Clinical Findings

A. Symptoms and Signs

Nonfunctioning tumors typically present with mass effect and metastases, such as pancreatitis, jaundice, abdominal pain, or weight loss.

Insulinomas secrete insulin and present with the symptoms of fasting hypoglycemia. (See Chapter 27.)

Gastrinomas usually present with peptic ulcer disease—abdominal pain (75%), heartburn (44%), bleeding (25%)—or weight loss (17%) (Zollinger-Ellison syndrome). Endoscopy usually shows hyperplastic gastric rugae (94%).

Glucagonomas usually present with weight loss caused by glucagon-stimulated protein hepatic gluconeogenesis and related protein catabolism. Other common manifestations include diarrhea, nausea, peptic ulcer, hypoaminoacidemia, or necrotic migratory erythema, known as “glucagonoma syndrome.” Diabetes mellitus develops in about 35% of patients. The median survival is 34 months after diagnosis.

Somatostatinomas can present with a classic triad of symptoms: diabetes mellitus due to its inhibition of insulin and glucagon secretion; cholelithiasis due to its inhibition of gallbladder motility; and steatorrhea due to its inhibition of pancreatic exocrine function. Diarrhea, hypochlorhydria, and anemia can also occur.

VIPomas present with profuse watery diarrhea (unremitting), hypokalemia, and achlorhydria (“WDHA”), the so-called Verner-Morrison syndrome.

CCKomas may present with liver metastases and symptoms of diarrhea, peptic ulcer disease, and weight loss.

Carcinoid tumors can produce “carcinoid syndrome”: episodes of abdominal pain, diarrhea, bronchospasm, and weight loss. Dry skin and flushing typically affect the upper chest, neck, and face and lasts from 30 seconds to 30 minutes, although flushing with bronchial carcinoids can persist for days. Although abdominal pain and diarrhea may occur at the same time as flushing, they usually occur at other times. Flushing can be unprovoked or precipitated by exercise, anesthesia, emotional stimuli, or foods (bananas, tomatoes, cheese, kiwi, eggplant, and alcohol). However, the full-blown carcinoid syndrome occurs with only about 10% of tumors. Other manifestations include carcinoid heart disease caused by endocardial fibrotic plaques. Tumor-induced fibrosis can also occur in the retroperitoneum causing ureteral obstruction or in the

penis causing Peyronie disease. Pellagra (glossitis, confusion, dry skin), which results from the conversion of tryptophan (a precursor to niacin) to serotonin by tumor cells, may develop in affected patients with widespread metastases.

Bronchial carcinoids secrete serotonin and can produce carcinoid syndrome even without hepatic metastases. Foregut carcinoids secrete serotonin that is hepatically metabolized and produce carcinoid syndrome only when they have metastasized to the liver. Appendiceal carcinoids are typically discovered incidentally during appendectomy; hemicolectomy is required if the tumor is 2 cm or larger or has unfavorable histopathology. Cecal carcinoids often present with intestinal obstruction or intestinal bleeding. Hindgut carcinoids rarely produce serotonin and do not cause carcinoid syndrome.

Ectopic hormones can be secreted by GEP-NETs. Ectopic ACTH secretion from bronchial carcinoids or pancreatic neuroendocrine tumors (pNETs) can produce Cushing syndrome.

B. Laboratory Findings

About 40% of GEP-NETs are functional, producing hormones that serve as tumor markers, which are important for diagnosis and follow-up. Insulinomas produce insulin, proinsulin and C-peptide. Gastrinomas secrete gastrin and “big” gastrin. Glucagonomas secrete glucagon and other hormones, including gastrin. For carcinoid tumors, serum serotonin may be elevated along with urinary 5-hydroindoleacetic acid (5-HIAA). Patients with CCKomas may have elevated serum levels of cholecystokinin and CgA.

C. Imaging

Localization of GEP-NETs and their metastases is best done with PET scanning using ⁶⁸Ga-DOTATATE, a radio-labeled somatostatin analog. For hepatic metastases, MRI scanning is more sensitive than CT.

For insulinomas, preoperative localization studies are less successful and have the following sensitivities: ultrasonography 25%, CT 25%, endoscopic ultrasonography 27%, transhepatic portal vein sampling 40%, and arteriography 45%. Nearly all insulinomas can be successfully located at surgery by the combination of intraoperative palpation (sensitivity 55%) and ultrasound (sensitivity 75%), and ⁶⁸Ga-DOTATATE-PET (sensitivity 90%). Tumors may be located in the pancreatic head or neck (57%), body (15%), or tail (19%) or in the duodenum (9%). MRI is used to screen members of kindreds with genetic syndromes that predispose them to GEP-NETs.

Treatment

Surgery is the primary initial treatment for most GEP-NETs and is a reasonable option even for patients with stage IV disease. The aggressiveness of the surgery may vary from conservative debulking to radical resection and even liver transplantation. However, incidentally discovered nonfunctioning pNETs that are asymptomatic and smaller than 2 cm are increasingly being monitored without surgery. Another treatment option for pNETs is

endoscopic ultrasound-guided radiofrequency ablation (EUS-RFA) that induces thermal necrosis of the tumor.

With gastrinomas, the gastric hyperacidity of Zollinger-Ellison syndrome is treated with a proton pump inhibitor at quadruple the usual doses. Proton pump inhibitors increase serum gastrin, which would otherwise be useful as a tumor marker for gastrinoma recurrence after surgical resection.

Tumor visualization on ⁶⁸Ga-DOTATATE-PET imaging indicates that they may respond to long-acting preparations of somatostatin analogs, including lanreotide (Somatuline Depot) and octreotide (Sandostatin LAR Depot). Subcutaneous injections of Octreotide LAR 20–30 mg are required every 4 weeks. Treatment improves symptoms in patients with functioning tumors and also appears to improve progression-free survival in patients with either functioning or nonfunctioning GEP-NETs. Enlarging hepatic metastases may be embolized with ⁹⁰Y-labeled resin or glass microspheres. For patients with progressive metastatic disease, chemotherapy (eg, everolimus) improves progression-free survival when added to somatostatin analog therapy (Table 39–2). Patients with GEP-NETs that continue to progress may be treated with PRRT, usually with four separate infusions of ¹⁷⁷Lu-DOTATE (Lutathera).

Prognosis

The prognosis for patients with GEP-NETs is variable, depending on the tumor grade and stage. Patients with well or moderately well differentiated GEP-NETs (Ki-67, a marker for cellular proliferation, less than 20%) have a better survival than those with poorly differentiated tumors. Smaller tumors without detectable metastases have a much lower chance of recurrence after surgery. However, most patients with GEP-NETs are stage IV with hepatic metastases by the time of diagnosis. Nevertheless, low-grade metastases may be indolent or slow-growing and may respond to octreotide or lanreotide. The overall prognosis for patients with GEP-NETs is much better than that for adenocarcinomas that arise from the same organs. The prognosis is worse for patients with serum pancreatic polypeptide levels above 500 pmol/L, since it correlates with the amount of hepatic metastases.

The surgical complication rate for GEP-NETs is about 40%, with patients commonly developing fistulas and infections. Extensive pancreatic resection may cause diabetes mellitus. EUS-RFA is effective for most patients with pNETs up to 3 cm, even those with multiple tumors. Patients with insulinomas usually experience correction of hypoglycemia within 1 hour following this procedure. However, the long-term response rate is unknown. For patients with gastrinomas, the 5-, 10-, and 20-year survival rates with MEN 1 are 94%, 75%, and 58%, respectively, while the survival rates for patients with sporadic gastrinomas are 62%, 50%, and 31%, respectively. Decreased overall survival has been noted with the following: higher stage and grade of tumor, male sex, age over 60 years, unmarried status, nonfunctioning tumor, location of tumor in pancreatic head, and lack of surgical treatment.

Bonds M et al. Neuroendocrine tumors of the pancreatobiliary and gastrointestinal tracts. *Surg Clin North Am.* 2020;100:635. [PMID: 32402306]

MULTIPLE ENDOCRINE NEOPLASIA (MEN)

MEN TYPES 1—4



ESSENTIALS OF DIAGNOSIS

- ▶ **MEN 1:** tumors of the parathyroid glands, endocrine pancreas and duodenum, anterior pituitary, adrenal, thyroid; carcinoid tumors; lipomas and facial angiofibromas.
- ▶ **MEN 2:** medullary thyroid cancer, hyperparathyroidism, pheochromocytoma, Hirschsprung disease.
- ▶ **MEN 3:** medullary thyroid cancer, pheochromocytoma, Marfan-like habitus, mucosal neuromas, intestinal ganglioneuroma, delayed puberty.
- ▶ **MEN 4:** tumors of the parathyroid glands, anterior pituitary gland, adrenal gland, ovary, testicle, kidney.

Syndromes of MEN are inherited as autosomal dominant traits that cause a predisposition to the development of tumors of two or more different endocrine glands (Table 26–12). MEN syndromes are caused by germline mutations and tumors arising when additional somatic mutations occur in predisposed organs. Patients with MEN should have genetic testing so that their first-degree relatives may then be tested for the specific mutation.

1. MEN 1

Multiple endocrine neoplasia type 1 (MEN 1, Wermer syndrome) is a tumor syndrome with a prevalence of 2–10 per 100,000 persons in the United States. About 90% of affected patients harbor a detectable germline mutation in the *menin* gene.

The presentation of MEN 1 is variable, even in the same kindred. Affected patients are prone to many different tumors, particularly involving the parathyroids, endocrine pancreas and duodenum, and anterior pituitary (Table 26–12). Incidental adrenal nodules are found in about 50% of affected patients but are rarely secretory. The initial biochemical manifestations (usually hypercalcemia) can often be detected as early as age 14–18 years in patients with a MEN 1 gene mutation, although clinical manifestations usually present in the third or fourth decade.

Hyperparathyroidism is the first clinical manifestation of MEN 1 in two-thirds of affected patients, but it may present at any time of life.

GEP-NETs and carcinoids occur in up to 70% of patients with MEN 1. The GEP-NETs may secrete only pancreatic polypeptide or be nonsecretory altogether (20–55%). Gastrinomas occur in about 40% of patients with MEN 1. Concurrent hypercalcemia, due to hyperparathyroidism in MEN 1, stimulates gastrin and worsens gastric acid secretion; control of the hypercalcemia often reduces serum gastrin levels and gastric acid secretion. Carcinoid tumors can arise in the lung or abdomen and can metastasize, especially to the liver.

Insulinomas occur in about 10% of patients with MEN 1. Extrapancreatic neuroendocrine tumors are common in MEN 1, are frequently malignant, and include carcinoid tumors usually in foregut locations (69%), such as the lung, thymus, duodenum, or stomach.

Pituitary adenomas are the presenting tumor in 29% of patients with MEN 1 and eventually are found in about

Table 26–12. Multiple endocrine neoplasia (MEN) syndromes: incidence of tumor types.

Tumor Type	MEN 1	MEN 2 (MEN 2A)	MEN 3 (MEN 2B)	MEN 4
Parathyroid	95%	20–50%	Rare	Common
Pancreatic	54%			Common
Pituitary	42%			Common
Medullary thyroid carcinoma		> 90%	80%	
Pheochromocytoma	Rare	20–35%	60%	
Mucosal and gastrointestinal ganglioneuromas		Rare	> 90%	
Subcutaneous lipoma	30%			
Adrenocortical adenoma	30%			Common
Thoracic carcinoid	15%			
Thyroid adenoma	55%			Common
Facial angiofibromas and collagenomas	85%			
Breast cancer	27%			

42% of patients with MEN 1. About 42% of such pituitary adenomas are nonsecretory. While nonsecretory pituitary microadenomas (less than 1 cm and detected on routine MRI screening) are usually indolent, about 25% of nonsecretory pituitary adenomas are macroadenomas (1 cm or more) and more aggressive.

Adrenal adenomas or hyperplasia occur in about 40% of patients with MEN 1 and 50% are bilateral. They are generally benign and nonfunctional. These adrenal lesions are ACTH-independent.

Thymic neuroendocrine tumors occur in 3.4% of affected patients, mostly in males, with a 10-year survival of 25%. Lung neuroendocrine tumors occur in 13%, with a 10-year survival of 71%.

Benign thyroid adenomas or multinodular goiter occurs in about 55% of MEN 1 patients who may undergo a thyroidectomy at the time of parathyroidectomy.

Nonendocrine tumors occur commonly in MEN 1, particularly small head-neck angiofibromas (85%) and lipomas (30%). Collagenomas are common (70%), presenting as firm dermal nodules. Breast cancer risk is increased over two-fold. Breast cancer tends to present earlier; cancer surveillance is recommended in women beginning by age 40 years, optimally using MRI. Affected patients may also be more prone to meningiomas, breast cancer, colorectal cancers, prostate cancer, and malignant melanomas.

Overall, patients with MEN 1 have an increased mortality rate with a mean life expectancy of only 55 years.

2. MEN 2 (formerly MEN 2A)

Multiple endocrine neoplasia type 2 (MEN 2A, Sipple syndrome) is a rare autosomal-dominant tumor syndrome that arises in patients with a germline gain-of-function *ret* protooncogene mutation. Genetic testing identifies about 95% of affected individuals.

Medullary thyroid carcinoma (greater than 90%); hyperparathyroidism (30%), with hyperplasia or adenomas of multiple parathyroid glands developing in most cases; pheochromocytomas (30%), which are often bilateral and frequently asymptomatic; and Hirschsprung disease may develop. No patients with MEN 2 should receive therapy for diabetes with glucagon-like peptide 1 (GLP 1) agonists that may increase the risk for medullary thyroid carcinoma. Before any surgical procedure, MEN 2 (2A) carriers should be screened for pheochromocytoma (see above) and for medullary thyroid carcinoma.

3. MEN 3 (formerly MEN 2B)

Multiple endocrine neoplasia type 3 (MEN 2B) is a familial, autosomal dominant multiglandular syndrome that is also caused by a germline gain-of-function mutation of the *ret* protooncogene. MEN 3 (2B) is characterized by mucosal neuromas (in more than 90% of cases) with bumpy and enlarged lips and tongue, Marfan-like habitus (75% of

cases), and adrenal pheochromocytomas (60%) that are rarely malignant and often bilateral. Patients also have intestinal abnormalities (75%) such as intestinal ganglioneuromas, skeletal abnormalities (87%), and delayed puberty (43%). Medullary thyroid carcinoma (80%) is aggressive and presents early in life.

4. MEN 4

Multiple endocrine neoplasia type 4 (MEN 4) is a rare autosomal-dominant familial tumor syndrome caused by germline mutations in the gene *CDKN1B*. Affected patients are particularly prone to parathyroid adenomas (80%), pituitary adenomas (less aggressive than those seen with MEN 1), pancreatic neuroendocrine tumors, and adrenal tumors. Unlike patients with MEN 1, those with MEN 4 are also prone to renal tumors, testicular cancer, neuroendocrine cervical carcinoma, and primary ovarian failure.

Kiernan CM et al. Surgical management of multiple endocrine neoplasia 1 and multiple endocrine neoplasia 2. *Surg Clin North Am.* 2019;99:693. [PMID: 31255200]

McDonnell JE et al. Multiple endocrine neoplasia: an update. *Intern Med J.* 2019;49:954. [PMID: 31387156]

OTHER SYNDROMES OF MULTIPLE ENDOCRINE NEOPLASIA

Patients with **Carney complex** develop adrenocortical nodular hyperplasia that can produce skin abnormalities, Cushing syndrome, GH-secreting pituitary adenomas or hyperplasia with acromegaly, thyroid tumors, gonadal Sertoli cell tumors, myxomas of the heart and breast, and other malignancies. With **McCune-Albright syndrome**, precocious puberty (particularly girls) develops due to gonadal hypersecretion. Multiple adrenal nodules can rarely cause Cushing syndrome. Hyperthyroidism results from autonomously functioning thyroid nodules. Acromegaly is caused by GH-secreting pituitary tumors. Patients also have fibrous dysplasia of bones and hypophosphatemia, and bone fractures are common. Sudden death has been reported. **Type 2 von Hippel Lindau (VHL) syndrome** is associated with pheochromocytomas, pancreatic/duodenal neuroendocrine tumors, hyperparathyroidism, and pituitary tumors as well as hemangiomas and renal cell carcinomas. **Hypoxia inducible factor 2A (HIF2A) germline mutations** predispose to pheochromocytomas, pancreatic/duodenal somatostatinomas, as well as erythrocytosis and retinal abnormalities. **Neurofibromatosis type 1 (NF-1)** is associated with pheochromocytomas and pancreatic/duodenal somatostatinomas as well as neurofibromas and hypothalamic hamartomas. **Beckwith Wiedemann syndrome** is associated with an increased risk of malignancies, particularly Wilms tumor and hepatoblastoma, but also neuroblastoma, adrenocortical carcinoma, pheochromocytoma, and paraganglioma.

DISEASES OF THE TESTES & MALE BREAST

MALE HYPOGONADISM



ESSENTIALS OF DIAGNOSIS

- ▶ Diminished libido and erections.
- ▶ Fatigue, depression, reduced exercise endurance.
- ▶ Testes small or normal in size.
- ▶ Low serum total testosterone or free testosterone.
- ▶ Hypogonadotropic hypogonadism: low or normal serum LH and FSH.
- ▶ Hypergonadotropic hypogonadism: testicular failure, high serum LH and FSH.

► General Considerations

Male hypogonadism is caused by deficient testosterone secretion by the testes. It may be classified according to whether it is due to (1) insufficient gonadotropin secretion by the pituitary (hypogonadotropic); (2) pathology in the testes themselves (hypergonadotropic); or (3) both (Table 26–13). Partial male hypogonadism may be difficult to distinguish from the physiologic reduction in serum testosterone seen in normal aging, obesity, and illness.

► Etiology

A. Hypogonadotropic Hypogonadism (Low Testosterone With Normal or Low LH)

A deficiency in FSH and LH may be isolated or associated with other pituitary hormonal abnormalities. (See Hypopituitarism.) Hypogonadotropic hypogonadism can be primary, defined as failure to enter puberty by age 14, or it can be acquired. Causes of primary hypogonadotropic hypogonadism include isolated hypogonadotropic hypogonadism, hypopituitarism, or simple constitutional delay of growth and puberty. Causes of apparently acquired etiologies include genetic conditions (eg, Kallmann syndrome or *PROKR2* mutations, X-linked congenital adrenal hypoplasia, 17-ketosteroid reductase deficiency, Prader-Willis syndrome), which account for about 40% of cases of isolated, and apparently idiopathic, acquired hypogonadotropic hypogonadism with a serum testosterone level less than 150 ng/dL (5.2 nmol/L) (Table 26–13).

Partial male hypogonadotropic hypogonadism is defined as a serum testosterone in the range of 150–300 ng/dL (5.2–10.4 nmol/L). The main causes of acquired partial male hypogonadotropic hypogonadism include obesity, poor health, or normal aging, such that it is termed **age-related hypogonadism**. However, other causes need to be excluded, including pituitary or hypothalamic tumors. Spermatogenesis is usually preserved.

Table 26–13. Causes of male hypogonadism.

Hypogonadotropic (Low or Normal LH)	Hypergonadotropic (High LH)
Aging	Aging
Alcohol	Autoimmunity
Chronic illness	Anorchia (bilateral)
Constitutional delay of growth and puberty	Chemotherapy
Cushing syndrome	Idiopathic
Drugs	Klinefelter syndrome
Estrogen	Leprosy
GnRH agonist (leuprolide)	Lymphoma
Ketoconazole	Male climacteric
Marijuana	Myotonic dystrophy
Opioids (oral, injected, or intrathecal)	Noonan syndrome
Prior androgens	Orchiectomy (bilateral or unilateral)
Spironolactone	Orchitis
Genetic conditions ¹	Radiation or radioisotope therapy
Granulomatous diseases	Sertoli cell-only syndrome
Hemochromatosis	Testicular trauma
Hypopituitarism	Tuberculosis
Hypothalamic or pituitary tumors	Uremia
Hypothyroidism, hyperthyroidism	Viral infections (mumps)
Idiopathic	XY gonadal dysgenesis
Kidney disease	
Lymphocytic hypophysitis	
Major medical or surgical illnesses	
Malnourishment	
Obesity (BMI > 30 kg/m ²)	

¹See text for discussion.

BMI, body mass index; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

B. Hypergonadotropic Hypogonadism (Testicular Failure With High LH)

A failure of the testicular Leydig cells to secrete adequate testosterone causes a rise in LH and FSH. Acquired conditions that can cause testicular failure are listed in Table 26–13. Male hypergonadotropic hypogonadism can be caused by XY gonadal dysgenesis, partial 17-ketosteroid reductase deficiency and a congenital partial deficiency in the steroidogenic enzyme CYP17 (17-hydroxylase). Abiraterone acetate, a drug for prostate cancer, inhibits CYP17. In men who have had a unilateral orchiectomy for cancer, the remaining testicle frequently fails, even in the absence of radiation or chemotherapy.

Klinefelter syndrome (47,XXY and its variants) is the most common chromosomal abnormality among males, with an incidence of about 1:500 (see Chapter 40). Although puberty occurs at the normal time, the degree of virilization is variable. Serum testosterone is usually low and gonadotropins are elevated. Other common findings include tall stature and abnormal body proportions that are unusual for hypogonadal men (eg, height more than 3 cm greater than arm span).

XY gonadal dysgenesis describes several conditions that result in the failure of the testes to develop normally. SRY is a gene on the Y chromosome that initiates male sexual development. Mutations in SRY result in testicular dysgenesis. Affected individuals lack testosterone, which results in sex reversal: female external genitalia with a blind vaginal pouch, no uterus, and intra-abdominal dysgenetic gonads. Affected individuals appear as normal girls until their lack of pubertal development and amenorrhea leads to the diagnosis. Intra-abdominal rudimentary testes have an increased risk of developing a malignancy and are usually resected.

C. Androgen Insensitivity

Partial resistance to testosterone is a rare condition in which phenotypic males have variable degrees of apparent hypogonadism, hypospadias, cryptorchism, and gynecomastia. Serum testosterone levels are normal.

► Clinical Findings

A. Symptoms and Signs

Hypogonadism that is congenital or acquired during childhood presents as delayed puberty. Men with acquired hypogonadism have variable manifestations, known as “testosterone deficiency syndrome.” Most men experience decreased libido. Others complain of erectile dysfunction, poor morning erection, or hot sweats. Men often have depression, fatigue, or decreased ability to perform vigorous physical activity. The presenting complaint may also be infertility, gynecomastia, headache, fracture, or other symptoms related to the cause or result of the hypogonadism. The patient’s history often gives a clue to the cause (Table 26–13).

Physical signs associated with hypogonadism may include decreased body, axillary, beard, or pubic hair, but only after years of severe hypogonadism. Men with hypogonadism lose muscle mass and gain weight due to an increase in subcutaneous fat. Examination should include measurements of arm span and height. Testicular size should be assessed with an orchidometer (normal volume is about 10–25 mL; normal length is usually over 6 cm). Testicular size may decrease but usually remains within the normal range in men with postpubertal hypogonadotropic hypogonadism, but it may be diminished with testicular injury or Klinefelter syndrome. The testes must also be palpated for masses, since Leydig cell tumors may secrete estrogen and present with hypogonadism, and examined for evidence of trauma, infiltrative lesions (eg, lymphoma), or infection (eg, leprosy, tuberculosis).

B. Laboratory Findings

The evaluation for hypogonadism begins with a morning (before 10 AM) serum testosterone and free testosterone measurement. In men with low serum testosterone levels, testing is repeated in order to confirm the diagnosis. Serum testosterone levels are low if they are confirmed to be less than 240 ng/dL (8.3 nmol/L). Serum free testosterone below 35 pg/mL (120 pmol/L) is considered low for men ages 18–69 or below 30 pg/mL (100 pg/L) for men ages 70 and over.

Normal ranges for serum testosterone have been derived from nonfasting morning blood specimens, which tend to be the highest of the day. Later in the day, serum testosterone levels can be 25–50% lower. Therefore, a serum testosterone drawn fasting or late in the day may be misleadingly below the “reference range.”

Serum testosterone levels in men are highest at age 20–30 years and slightly lower at age 30–40 years. After age 40, serum total testosterone declines variably by an average of 1–2% annually; serum free testosterone levels decline even faster, since sex hormone binding globulin increases with age. Serum levels of free testosterone are lower in men aged 40–70 compared with younger men, without any increase in serum LH. A problem with the diagnosis of age-related hypogonadism is that most laboratories provide reference ranges for testosterone that are derived from young men and may not provide age-adjusted reference ranges for serum testosterone and free testosterone. The main conditions that contribute to the general decline in serum testosterone with aging include obesity, illness, and opioids. After age 70, LH levels tend to rise, indicating a contribution of primary gonadal dysfunction with advancing age. Testing for serum free testosterone is especially important for detecting hypogonadism in elderly men, who generally have high levels of sex hormone binding globulin. A low serum testosterone or free testosterone should be verified with a repeat morning nonfasting assay, along with serum LH and PRL levels. Serum LH levels are high in patients with hypergonadotropic hypogonadism but low or inappropriately normal in men with hypogonadotropic hypogonadism or normal aging. High serum estradiol levels are seen in men with obesity-related hypogonadotropic hypogonadism.

Testosterone stimulates erythropoiesis in men, causing the normal red blood count range to be higher in men than in women; mild anemia is common in men with hypogonadism. For men with long-standing severe male hypogonadism, osteoporosis is common, so a bone densitometry is recommended.

1. Hypogonadotropic hypogonadism—A serum PRL determination is obtained to screen for a pituitary prolactoma and other pituitary/hypothalamic lesions, but serum PRL may be elevated for many other reasons (see Table 26–1). The serum estradiol level may be elevated in patients with cirrhosis and in rare cases of estrogen-secreting tumors (testicular Leydig cell tumor or adrenal carcinoma). Men with no discernible cause for hypogonadotropic hypogonadism should be screened for hemochromatosis. Adult men with hypogonadotropic hypogonadism should have an MRI of the pituitary/hypothalamus to search for a mass lesion in presence of one or more of the following: (1) severe hypogonadism (serum testosterone below 150 ng/mL or 5.2 nmol/L), (2) elevated serum PRL, (3) other pituitary hormone deficiencies, or (4) symptoms of a mass lesion (headaches or visual field deficits).

2. Hypergonadotropic hypogonadism—Men with hypergonadotropic hypogonadism have low serum testosterone levels with a compensatory increase in FSH and LH. Klinefelter syndrome can be confirmed by karyotyping or by

measurement of leukocyte XIST. Testicular biopsy is usually reserved for younger patients in whom the reason for primary hypogonadism is unclear.

Treatment

Testosterone replacement is reasonable for boys who have not entered puberty by age 14 years. It is also beneficial for most men with primary testicular failure (hypergonadotropic hypogonadism). Testosterone replacement or gonadal stimulation therapy is also warranted for men with severe hypogonadotropic hypogonadism of any etiology with serum testosterone levels less than 150 ng/mL (5.2 nmol/L). Testosterone therapy should also be considered for men with low or low-normal serum testosterone or free testosterone, along with elevated serum LH levels. For other men without elevated serum LH levels and an average of at least two morning serum total testosterone levels below 275 ng/dL (9.5 nmol/L, “physiologic hypogonadism”), a trial of testosterone therapy may be considered, particularly if they have at least three of the following six symptoms: erectile dysfunction, poor morning erection, low libido, depression, fatigue, and inability to perform vigorous activity. Testosterone replacement should be continued only if patients clearly derive clinical benefit from therapy. Therapy can be adjusted with an aim to improve clinical symptoms while maintaining normal serum levels of testosterone or free testosterone. Men with physiologic low-normal serum testosterone levels above 325 ng/dL (11.3 nmol/L) are unlikely to benefit from testosterone therapy.

Testosterone replacement or stimulation therapy carries certain risks. Therefore, testosterone therapy should only be given to men who have documented low levels of serum total or free testosterone. Testosterone therapy should not be given to men with active breast cancer or prostate cancer. It is also prudent to monitor the hematocrit and lipid profile of men receiving testosterone, since therapy can cause erythrocytosis and hyperlipidemia. Testosterone therapy can also cause gynecomastia. Testosterone therapy is not given to men with untreated sleep apnea or heart failure.

Drug interactions can occur. Testosterone should be administered cautiously to men receiving coumadin, since the combination can increase the INR and risk of bleeding. Similarly, testosterone therapy can increase serum levels of cyclosporine, tacrolimus, and tolvaptan. Testosterone can predispose to hypoglycemia in diabetic men receiving insulin or oral hypoglycemic agents, so close monitoring of blood sugars is advisable during initiation of testosterone therapy.

Men with severe osteoporosis may require treatment with bisphosphonates and vitamin D, in addition to testosterone replacement therapy.

A. Therapies for Male Hypogonadism

1. Testosterone topical gels—Topical testosterone is usually applied once daily in the morning after showering. One or two fingers are used to apply the gel evenly to skin. Afterwards, the hands should be washed. Topical testosterone should not be applied to the breast or genitals. The gel should be allowed to air-dry (about 10 minutes) before

dressing. Before close contact with people, a shirt must be worn or the areas of application washed with soap and water to prevent transfer of testosterone to them. The patient should avoid swimming, showering, or washing the application area for at least 2 hours following application.

Testosterone topical generic 1% gel is available in packets (12.5 mg/1.25 g, 25 mg/2.5 g, or 50 mg/5 g) or tubes (50 mg/5 g). The recommended dose is 50–100 mg daily. Testosterone topical generic 2% gel is available in a gel pump (10 mg/0.5 g actuation). The recommended dose is 40–70 mg daily. Androgel 1% gel is available in 2.5-g packets (25 mg testosterone) and 5-g packets (50 mg testosterone) and in a pump that dispenses 12.5 mg testosterone per pump actuation; the recommended dose is 50–100 mg applied daily to the shoulders. Androgel 1.6% gel is available in a pump that dispenses 20.25 mg testosterone per pump actuation; the recommended dose is 40.5–81 mg daily. Testim 1% gel is available in 5-g tubes (50 mg testosterone); the recommended dose is 50–100 mg applied daily. Fortesta 2% gel is available in a pump that dispenses 10 mg testosterone per pump actuation; the recommended dose is 40–70 mg daily. Testogel (not available in the United States) is distributed in 5-g sachets (50 mg testosterone). Testim, Fortesta, and Testogel may be applied to shoulders, upper arms, or abdomen. Axiron 2% solution is available in a pump that dispenses 30 mg per actuation; the recommended dose is 30–60 mg applied to each axilla daily. Vogelxo is a 1% testosterone gel that is available in packets or tubes (50 mg/5 g) or a gel pump (12.5 mg/1.25 g); it is applied to the shoulders in doses of 50–100 mg once daily.

The serum testosterone level should be determined about 14 days after starting therapy; if the level remains below normal or the clinical response is inadequate, the daily dose may be increased to 1.5 to 2 times the initial dose. Unfortunately, serum testosterone levels vary considerably during the day after topical testosterone gel application, such that a single serum testosterone level may not accurately reflect the average serum testosterone for that individual.

2. Transdermal testosterone patches—Testosterone transdermal systems (skin patches) are applied to nongenital skin. Androderm (2 or 4 mg/day) patches may be applied at bedtime in doses of 4–8 mg; they adhere tightly to the skin and may cause skin irritation.

3. Parenteral testosterone—The dose and injection intervals are adjusted according to the patient’s clinical response and serum testosterone levels drawn just before the next injection is due. A target serum testosterone level of 500 ng/dL (17.3 nmol/L) is suggested. **Testosterone cypionate** has been in use for decades; it is an intramuscular testosterone formulation that is available in solutions containing 200 mg/mL. Its main advantage is low cost. The usual dose is 200 mg every 2 weeks or 300 mg every 3 weeks. It is usually injected into the gluteus medius muscle in the upper lateral buttock, alternating sides. The injection technique must include sterile precautions and draw-back prior to injection to ensure against intravenous injection, which can result in pulmonary oil embolism.

Testosterone pellets (Testopel) are a long-lasting depot testosterone formulation that is available as individual vials

containing a single 75-mg implantable pellet in each vial. With sterile technique, the skin of the upper-outer buttock is anesthetized with lidocaine; using a trochar, the pellets are injected subcutaneously in doses of 150–450 mg every 3–6 months as an in-office procedure.

Testosterone undecanoate (Aveed) is a long-lasting depot testosterone formulation. Its use is restricted to qualified health care facilities. It is usually injected into the gluteus medius muscle in the upper lateral buttock, alternating sides. A serum testosterone level is measured before the fourth dose; if the serum testosterone remains low, the dosing interval is shortened to every 10 weeks.

Caution: Testosterone undecanoate injections have caused serious pulmonary oil microembolism reactions that present with cough, dyspnea, tight throat, chest pain, and syncope. Anaphylaxis can also occur. *Patients must be observed in the health care setting for 30 minutes after the injection in order to provide appropriate medical care for the complication.*

4. Buccal testosterone—Testosterone buccal tablets (Striant) are placed between the upper lip and gingivae. One or two 30-mg tablets are thus retained and changed every 12 hours. They should not be chewed or swallowed. It is not available in the United States.

5. Testosterone nasal gel—Intranasal gel testosterone (Natesto) is self-administered by a metered-dose nasal pump: one pump actuation (5.5 mg) into each nostril three times daily. The nasal pump needs to be primed by inverting it and pressing the pump 10 times before it is used the first time. It should not be used concurrently with intranasal sympathomimetic decongestants. Adverse effects include nasopharyngitis, sinusitis, bronchitis, epistaxis, nasal discomfort, and headache.

6. Clomiphene citrate—Men with functional hypogonadotropic hypogonadism usually respond well to clomiphene citrate that is administered orally in doses that are titrated to achieve the desired clinical response with a serum testosterone level of about 500 ng/dL (17.3 nmol/L). Begin with clomiphene 25 mg on alternate days and increased to 50 mg on alternate days if necessary, with a maximum dose of 50 mg daily. Serum testosterone levels usually normalize while spermatogenesis usually improves.

7. Gonadotropins—Patients with hypogonadotropic hypogonadism may require therapy with gonadotropins, particularly to induce fertility. Men may receive hCG 1000 units subcutaneously three times weekly for 6 months; if the semen analysis shows inadequate sperm, FSH 75 units subcutaneously three times weekly is added. Many men prefer long-term therapy with hCG over testosterone therapy, but cost is an issue.

8. Oral testosterone undecanoate—An oral preparation of testosterone undecanoate (Jatenzo) is available in capsules of 158 mg, 198 mg, and 237 mg and should be taken with food. The starting dose is 237 mg twice daily and can be increased to a maximum of 792 mg daily, with adjustments according to clinical response and serum testosterone levels obtained 3–4 hours (peak) after an oral dose.

Serum testosterone falls to low levels by 12 hours after an oral dose; dosing every 8 hours may produce more consistent serum testosterone levels. Side effects are those of nonoral testosterone with additional side effect including gastrointestinal intolerance and an increase in systolic blood pressure (average 4 mm Hg).

9. Oral methyltestosterone—Oral methyltestosterone is available as 10 mg tablets. It has a short half-life of 3 hours, so it is usually taken in divided doses up to a total of 10–50 mg daily. Side effects include acute hepatitis and long-term high-dose use can cause peliosis hepatitis, cholestatic hepatitis, and hepatocellular carcinoma. Therefore, its use is not recommended, and it is no longer available in some countries.

10. Weight loss—When hypogonadotropic hypogonadism is due to morbid obesity, significant weight loss will improve serum testosterone levels. The rise in serum testosterone is proportionate to the weight loss. Although diet-induced weight loss is beneficial, bariatric surgery has been much more effective and serum testosterone levels may normalize after dramatic weight loss.

B. Benefits of Testosterone Replacement Therapy

Testosterone therapy given for the indications listed under Treatment, above, usually benefits men with low serum testosterone and at least three manifestations of hypogonadism. Replacement testosterone therapy can improve overall mood, sense of well-being, sexual desire, and erectile function. It also increases physical vigor and muscle strength. Testosterone replacement improves exercise endurance and stair climbing ability. Long-term testosterone replacement causes significant weight loss and a reduction in waist circumference. After 2 years of testosterone replacement, muscle mass increases about 4.5%, while fat mass decreases by about 9.1%. Appropriate testosterone replacement therapy also appears to improve longevity.

C. Risks of Testosterone Replacement or Stimulation Therapy

Testosterone therapy does not appear to significantly increase the risk of prostate cancer or benign prostatic hypertrophy above that of normal men, as long as serum testosterone levels are maintained in the normal reference range on therapy. However, testosterone therapy is contraindicated in the presence of active prostate cancer. Hypogonadal men who have had a prostatectomy for low-grade prostate cancer, and who have remained in complete remission for several years, may have testosterone therapy given cautiously while monitoring serum PSA levels.

Erythrocytosis develops in some men who are treated with testosterone. Erythrocytosis is more common with intramuscular injections of testosterone enanthate than with transcutaneous testosterone. Testosterone replacement has not been considered to significantly increase the risk of thromboembolic events in most hypogonadal men. However, one large medical database study has found a correlation between testosterone therapy and thromboembolic events, particularly in men with a prior history of

vascular events and in men being prescribed testosterone without proper documentation of hypogonadism.

Testosterone therapy tends to aggravate sleep apnea in older men, likely through CNS effects. Surveillance for sleep apnea is recommended during testosterone therapy and a formal evaluation is recommended for all high-risk patients with snoring, obesity, partner's report of apneic episodes, nocturnal awakening, unrefreshing sleep with daytime fatigue, or hypertension.

Testosterone therapy frequently increases acne that is usually mild and tolerated; topical antiacne therapy or a reduction in testosterone replacement dosage may be required. Increases in intraocular pressure have occurred during testosterone therapy. During the initiation of testosterone replacement therapy, gynecomastia develops in some men, which usually is mild and tends to resolve spontaneously; switching from testosterone injections to testosterone transdermal gel may help this condition.

D. Risks of Performance-Enhancing Anabolic Steroids

Performance-enhancing agents, particularly androgenic anabolic steroids, are used by up to 2% of young athletes and by 20–65% of power sport athletes. They are often used as part of a “stacking” polypharmacy that may include nandrolone decanoate, dimethandrolone, testosterone propionate, or testosterone enanthate. These androgens are usually illegal, often contaminated by toxic substances (such as arsenic), and can produce toxic hepatitis, dependence, aggression, depression, dyslipidemias, gynecomastia, acne, male pattern baldness, hepatitis, thromboembolism, and cardiomyopathy. Arsenic contamination can cause multi-organ failure and death.

► Prognosis of Male Hypogonadism

If hypogonadism is due to a pituitary lesion, the prognosis is that of the primary disease (eg, tumor, necrosis). The prognosis for restoration of virility is good if testosterone is given. In one large study, cardiovascular risk was reduced in hypogonadal men over age 40 who were receiving testosterone replacement therapy to maintain serum testosterone levels within the normal reference range.

Bhasin S et al. Testosterone therapy in men with hypogonadism: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2018;103:1715. [PMID: 29562364]

Diem SJ et al. Efficacy and safety of testosterone treatment in men: an evidence report for a clinical practice guideline by the American College of Physicians. *Ann Intern Med.* 2020;172:1184. [PMID: 31905375]

Glinborg D et al. Testosterone replacement therapy of opioid-induced male hypogonadism improved body composition but not pain perception; a double-blind, randomized, and placebo-controlled trial. *Eur J Endocrinol.* 2020;182:539. [PMID: 32213659]

McGriff SC et al. Optimal endocrine evaluation and treatment of male infertility. *Urol Clin North Am.* 2020;47:139. [PMID: 32272985]

Salter CA et al. Guideline of guidelines: testosterone therapy for testosterone deficiency. *BJU Int.* 2019;124:722. [PMID: 31420972]

Walker RF et al. Association of testosterone therapy with risk of venous thromboembolism among men with and without hypogonadism. *JAMA Intern Med.* 2020;180:190. [PMID: 31710339]

CRYPTORCHISM

Cryptorchidism is found in 1–2% of males after 1 year of age but must be distinguished from retractile testes, which require no treatment. Infertility or subfertility occurs in up to 75% of men with bilateral cryptorchism and in 50% of men with unilateral cryptorchism. Some patients have underlying hypogonadism, including hypogonadotropic hypogonadism.

For a testis that is not palpable, it is important to locate the testis and bring it into the scrotum or prove its absence. About one-third of nonpalpable testes are located within the inguinal canal, one-third are intra-abdominal, and one-third are absent. Ultrasound can detect an inguinal testis. If ultrasound is negative, MRI is performed to locate the testis.

The lifetime risk of testicular neoplasia is 0.002% in healthy males. The risk of malignancy is higher for cryptorchid testes (0.06%) and for intra-abdominal testes (5%). Orchiopexy decreases the risk of neoplasia when performed before 10 years of age. For bilateral undescended testes, boys with early orchiopexy (before age 13 years) appear to have relatively normal fertility, whereas boys with delayed orchiopexy may have reduced fertility. With a unilateral undescended testis, about 50% descend spontaneously and early orchiopexy does not improve fertility, so orchiopexy is usually delayed until after puberty. For intra-abdominal testes, orchectomy after puberty is usually the best option.

Hildorf S et al. Fertility potential is compromised in 20% to 25% of boys with nonsyndromic cryptorchidism despite orchiopexy within the first year of life. *J Urol.* 2020;203:832. [PMID: 31642739]

GYNECOMASTIA

ESSENTIALS OF DIAGNOSIS

- Palpable enlargement of the male breast, often asymmetric or unilateral.
- Glandular gynecomastia: typically tender.
- Fatty gynecomastia: typically nontender.
- Must be distinguished from carcinoma or mastitis.

► General Considerations

Gynecomastia is defined as the presence of palpable glandular breast tissue in males. Gynecomastia is a common condition and its incidence appears to be increasing in all age groups. The causes are multiple and diverse

(Table 26–14). Pubertal gynecomastia develops in about 60% of boys; the swelling usually subsides spontaneously within a year. It is particularly common in teenagers who are very tall or overweight. About 20% of adult gynecomastia is caused by drug therapy. It can develop in HIV-infected patients treated with antiretroviral therapy, especially in men receiving efavirenz or didanosine; breast enlargement resolves spontaneously in 73% of patients within 9 months. Gynecomastia develops in about 50% of athletes who abuse androgens and anabolic steroids. Fatty pseudogynecomastia is common among elderly men, particularly when there is associated weight gain. However, true glandular gynecomastia can be the first sign of a serious disorder in older men (Table 26–14).

Table 26–14. Causes of gynecomastia.

Physiologic causes	Anti-androgens Aging Neonatal period, puberty Obesity
Endocrine diseases	Antipsychotics (first- and second-generation) Antiretroviral agents Calcium channel blockers (rare) Chorionic gonadotropin Cimetidine Clomiphene Diazepam Digitalis preparations Dutasteride, finasteride Estrogens (oral or topical) Ethionamide Famotidine (rare) Fenofibrate (rare) GH GnRH analogs Hydroxyzine Isoniazid Ketoconazole Lavender and tea tree oil (topical) Marijuana Methadone Methyldopa Metoclopramide Metronidazole Opioids Phenothiazines Progestins Proton pump inhibitors (uncommon) Selective serotonin reuptake inhibitors (SSRIs) Soy ingestion Statins (rare) Spironolactone (common) Sunitinib Tea tree oil (topical) Tricyclics
Systemic diseases	Androgen insensitivity syndrome Aromatase excess syndrome (sporadic or familial) Diabetic lymphocytic mastitis Hyperprolactinemia Hyperthyroidism or hypothyroidism Klinefelter syndrome Male hypogonadism (primary or secondary) Partial 17-ketosteroid reductase deficiency
Neoplasms	Chronic liver disease Chronic kidney disease Hansen disease Neurologic disorders Refeeding after starvation Spinal cord injury
Drugs (partial list)	Adrenal tumors Bronchogenic carcinoma Breast carcinoma Ectopic hCG: CNS germinoma, lung, hepatocellular, gastric, renal carcinomas Pituitary prolactinoma Testicular hCG-secreting tumors

GH, growth hormone; GnRH, gonadotropin-releasing hormone.

Clinical Findings

A. Symptoms and Signs

The male breasts must be palpated to distinguish firm true glandular gynecomastia from softer fatty pseudogynecomastia in which only adipose tissue is felt. The breasts are best examined both seated and supine. Using the thumb and forefinger as pincers, the subareolar tissue is compared to nearby adipose tissue. Fatty tissue is usually diffuse and nontender. True glandular enlargement beneath the areola may be tender. Pubertal gynecomastia is characterized by tender discoid enlargement of breast tissue 2–3 cm in diameter beneath the areola. The following characteristics are worrisome for malignancy: asymmetry; location not immediately below the areola; unusual firmness; or nipple retraction, bleeding, or discharge. The examination must also include an assessment of masculinization, examination of the testes for size and masses, and examination of the penis for hypospadias.

B. Laboratory Findings

In the presence of true glandular gynecomastia, laboratory studies should include liver biochemical tests, serum BUN, and creatinine. Endocrine testing, including serum testosterone, free testosterone, LH, FSH, TSH, and FT₄, is obtained to determine whether primary hypogonadism (low serum testosterone, high LH), secondary hypogonadism (low serum testosterone, low or normal LH), or androgen resistance may be present. High serum testosterone levels plus high LH levels characterize partial androgen insensitivity syndrome. A serum PRL is obtained to screen for hyperprolactinemia and pituitary/hypothalamic lesions. Serum beta-hCG and estradiol levels are obtained to screen for malignancy-associated gynecomastia. Detectable levels of beta-hCG implicate a testicular tumor (germ cell or Sertoli cell) or other malignancy (usually lung or liver). Increased serum estradiol levels may result from testicular tumors, increased beta-hCG, liver disease, obesity, adrenal tumors (rare), true hermaphroditism (rare), or aromatase gene gain-of-function mutations (rare). A karyotype for Klinefelter syndrome is obtained in men with persistent gynecomastia without obvious cause.

C. Imaging and Biopsy

Investigation of unclear cases should include bilateral mammography and a chest CT to search for bronchogenic or metastatic carcinoma. Benign mammographic findings make malignancy very unlikely. Suspicious mammographic findings require ultrasound-guided FNA and cytologic examination to distinguish gynecomastia from benign lesions (pseudogynecomastia, lipoma, posttraumatic hematoma/fat necrosis, epidermal inclusion cyst), lymphoma, and male breast cancer. Male breast cancer and gynecomastia may coexist.

Men with a high serum hCG or estradiol levels should have the test confirmed with repeat testing. Confirmed increased levels warrant a testicular ultrasound. If the testicular ultrasound is normal, high serum estradiol levels may warrant a CT of the adrenal glands; high serum hCG

levels may warrant additional CT scanning to detect rare hCG-secreting carcinomas of the lung, mediastinum, liver, stomach, or kidney.

Treatment

Pubertal gynecomastia often resolves spontaneously within 1–2 years. Drug-induced gynecomastia resolves after the offending drug is removed (eg, spironolactone stopped, with substitution of eplerenone). Patients with painful or persistent gynecomastia may be treated with medical therapy, usually for 9–12 months.

Selective estrogen receptor modulator (SERM) therapy is effective for true glandular gynecomastia. Raloxifene, 60 mg orally daily, may be more effective than tamoxifen.

Aromatase inhibitor (AI) therapy is also reasonably effective; anastrozole, 1 mg orally daily, reduces breast volume significantly over 6 months in adolescents. Serum estradiol levels fall slightly while serum testosterone levels rise. Long-term AI therapy in adolescents is not recommended because of the possibility of inducing osteoporosis and of delaying epiphyseal fusion, which could cause an increase in adult height.

Testosterone therapy for men with hypogonadism may improve or worsen preexistent gynecomastia.

Radiation therapy has been used prophylactically to prevent gynecomastia in men with prostate cancer being treated with antiandrogen therapy. Low-dose prophylactic radiation therapy reduces its incidence from 71% to 28%. Existing gynecomastia improves in 33% with radiation therapy. However, the long-term breast and other cancer risks of such radiation are unknown.

Surgical correction is reserved for patients with persistent or severe gynecomastia.

Ali SN et al. Which patients with gynaecomastia require more detailed investigation? Clin Endocrinol (Oxf). 2018;88:360. [PMID: 29193251]

Koch T et al. Marked increase in incident gynecomastia: a 20-year national registry study, 1998 to 2017. J Clin Endocrinol Metab. 2020;105:dgaa440. [PMID: 32754750]

HIRSUTISM & VIRILIZATION



ESSENTIALS OF DIAGNOSIS

- ▶ Hirsutism, acne, menstrual disorders.
- ▶ Virilization: muscularity, androgenic alopecia, deepening voice, clitoromegaly.
- ▶ Rarely, a palpable pelvic tumor.
- ▶ Serum DHEAS and androstenedione elevated in adrenal disorders; variable in others.
- ▶ Serum testosterone is often elevated.

General Considerations

Hirsutism is defined as cosmetically unacceptable terminal hair growth that appears in women in a male pattern.

Significant hirsutism affects about 5–10% of non-Asian women of reproductive age and over 40% of women at some point during their life. The amount of hair growth deemed unacceptable depends on a woman's ethnicity and cultural norms. Virilization is defined as the development of male physical characteristics in women, such as pronounced muscle development, deep voice, male pattern baldness, and more severe hirsutism.

Etiology

Hirsutism may be idiopathic or familial or be caused by the following disorders: polycystic ovary syndrome (PCOS), ovarian hyperthecosis, steroidogenic enzyme defects, neoplastic disorders; or rarely by medications, acromegaly, or ACTH-induced Cushing disease.

A. Idiopathic or Familial

Most women with hirsutism or androgenic alopecia have no detectable hyperandrogenism; hirsutism may be considered normal in the context of their genetic background. Such patients may have elevated serum levels of androstanediol glucuronide, a metabolite of dihydrotestosterone that is produced by skin in cosmetically unacceptable amounts.

B. Polycystic Ovary Syndrome (PCOS, Hyperthecosis, Stein-Leventhal Syndrome)

PCOS is a common functional disorder of the ovaries of unknown etiology (see Chapter 18). It accounts for at least 50% of all cases of hirsutism associated with elevated serum testosterone levels.

A diagnosis of PCOS must meet three criteria: (1) androgen excess with clinical hyperandrogenism or elevated serum free or total testosterone; (2) ovarian dysfunction with oligoanovulation or polycystic ovary morphology; and (3) absence of other causes of testosterone excess or anovulation such as pregnancy, thyroid dysfunction, 21-hydroxylase deficiency, neoplastic testosterone secretion, Cushing syndrome, or hyperprolactinemia.

Affected women usually have signs of hyperandrogenism, including hirsutism, acne, or male-pattern thinning of scalp hair; this persists after natural menopause. However, women of East Asian ancestry are less likely to exhibit hirsutism. Most women also have elevated serum testosterone or free testosterone levels. About 70% of affected women have polycystic ovaries on pelvic ultrasound and 50% have oligomenorrhea or amenorrhea with anovulation. Of note, about 30% of women with PCOS do *not* have cystic ovaries and 25–30% of normal menstruating women *have* cystic ovaries.

Obesity and high serum insulin levels (due to insulin resistance) contribute to the syndrome in 70% of women. The serum LH:FSH ratio is often greater than 2.0. Both adrenal and ovarian androgen hypersecretion are commonly present.

C. Steroidogenic Enzyme Defects

Congenital adrenal steroidogenic enzyme defects result in reduced cortisol secretion with a compensatory increase in

ACTH that causes adrenal hyperplasia. The most common enzyme defect is 21-hydroxylase deficiency, with a prevalence of about 1:18,000.

Partial deficiency in adrenal 21-hydroxylase can present in women as hirsutism. About 2% of patients with adult-onset hirsutism have been found to have a partial defect in adrenal 21-hydroxylase. The condition is more common in Ashkenazi Jews, Yupic Alaskans, and natives of La Reunion Island. The phenotypic expression is delayed until adolescence or adulthood; such patients do not have salt wasting. Polycystic ovaries and adrenal adenomas are more likely to develop in these women.

D. Neoplastic Disorders

Ovarian tumors are uncommon causes of hirsutism (0.8%) and include arrhenoblastomas, Sertoli-Leydig cell tumors, dysgerminomas, and hilar cell tumors. Adrenal carcinoma, a rare cause of Cushing syndrome and hyperandrogenism, can be quite virilizing. Pure androgen-secreting adrenal tumors occur very rarely; about 50% are malignant.

E. Rare Causes of Hirsutism & Virilization

Acromegaly and ACTH-induced Cushing syndrome are rare causes of hirsutism and virilization. Porphyria cutanea tarda can cause periorbital hair growth in addition to dermatitis in sun-exposed areas. Maternal virilization during pregnancy may result from a luteoma of pregnancy, hyperreactio luteinalis, or polycystic ovaries. In postmenopausal women, diffuse stromal Leydig cell hyperplasia is a rare cause of hyperandrogenism. Acquired hypertrichosis lanuginosa, which is diffuse fine lanugo hair growth on the face and body along with stomatologic symptoms, is usually associated with an internal malignancy, especially colorectal cancer, and may regress after tumor removal. Pharmacologic causes include minoxidil, cyclosporine, phenytoin, anabolic steroids, interferon, cetuximab, diazoxide, and certain progestins.

► Clinical Findings

A. Symptoms and Signs

Modest androgen excess from any source increases sexual hair (chin, upper lip, abdomen, and chest) and increases sebaceous gland activity, producing acne. Menstrual irregularities, anovulation, and amenorrhea are common. If androgen excess is pronounced, defeminization (decrease in breast size, loss of feminine adipose tissue) and virilization (frontal balding, muscularity, clitoromegaly, and deepening of the voice) occur. Virilization points to the presence of an androgen-producing neoplasm.

Hirsutism is quantitated using the Ferriman-Gallwey score; hirsutism is graded from 0 (none) to 4 (severe) in nine areas of the body (maximum possible score is 36) (<https://education.endocrine.org/ferriman-gallwey-hirsutism-system>). Scores below 8 are considered mild hirsutism and normal variants. Scores of 8–15 indicate moderate hirsutism. Scores over 15 indicate severe hirsutism. Of note, the normal score is lower in Asian women and higher in Mediterranean women.

A pelvic examination may disclose clitoromegaly or ovarian enlargement that may be cystic or neoplastic. Hypertension may be present in Cushing syndrome, adrenal 11-hydroxylase deficiency, or cortisol resistance syndrome.

B. Laboratory Testing and Imaging

Serum androgen testing is mainly useful to screen for rare occult adrenal or ovarian neoplasms. Testing is warranted for women with moderate to severe hirsutism, mild hirsutism with menstrual disturbances, and women with worsening hirsutism despite therapy.

Serum is assayed for total testosterone and free testosterone. A serum testosterone level greater than 200 ng/dL (6.9 nmol/L) or free testosterone greater than 40 ng/dL (140 pmol/L) indicates the need for a manual pelvic examination and ultrasound. If that is negative, an adrenal CT scan is performed. A serum androstenedione level greater than 1000 ng/dL (34.9 nmol/L) also points to an ovarian or adrenal neoplasm.

Patients with a serum DHEAS greater than 700 mcg/dL (35 nmol/L) have an adrenal source of androgen. This usually is due to adrenal hyperplasia and rarely to adrenal carcinoma. Patients with any clinical signs of Cushing syndrome should receive a screening test (eg, 1-mg overnight dexamethasone suppression test) (see Cushing Syndrome, above).

Screening for nonclassical “late-onset” congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is warranted for women with (1) high serum testosterone or free testosterone levels and (2) hirsutism with normal serum testosterone levels who are at high risk for CAH due to having a family history of hirsutism or being a member of a high-risk ethnic group (eg, Ashkenazi Jews, Croatians, Iranians, Yupik Inuit). The evaluation requires an early morning blood draw for serum 17-hydroxyprogesterone, ideally during the follicular (early) phase of the menstrual cycle or on a random day for women with irregular menses or amenorrhea. Patients with CAH usually have a baseline 17-hydroxyprogesterone level greater than 300 ng/dL (9.1 nmol/L). Serum levels of FSH and LH are elevated if amenorrhea is due to ovarian failure. An LH:FSH ratio greater than 2.0 is common in patients with PCOS. On abdominal ultrasound, about 25–30% of normal young women have polycystic ovaries, so the appearance of ovarian cysts on ultrasound is not helpful. Pelvic ultrasound or MRI usually detects virilizing tumors of the ovary. However, small virilizing ovarian tumors may not be detectable on imaging studies; selective venous sampling for testosterone may be used for diagnosis in such patients.

► Treatment

Any drugs causing hirsutism (see above) should be stopped. Any underlying medical causes of hirsutism (eg, Cushing syndrome, acromegaly) should be treated.

A. Laser and Topical Treatments

Local treatment of facial hirsutism is by shaving or depilatories, waxing, electrolysis, or bleaching. Eflornithine

(Vaniqa) 13.9% topical cream retards hair growth when applied twice daily to unwanted facial hair; improvement is noted within 4–8 weeks. Eflornithine may be used during laser therapy for a more dramatic response. However, local skin irritation may occur. Hirsutism returns with discontinuation, unless it is given with laser therapy.

Laser therapy (photoepilation) can be a very effective treatment for facial hirsutism, particularly for women with dark hair and light skin. For women of color, a longer-wavelength laser such as Nd:YAG or diode laser given with skin cooling is used. In such women, laser removal of facial hair significantly improves hirsutism. Repeated laser treatments are usually required. Accidental eye injuries have been reported; eye shields should be used during treatments. Laser therapy is not recommended for Middle Eastern and Mediterranean women with facial hirsutism, since they have a particularly increased risk of paradoxical hypertrichosis with laser therapy.

Topical minoxidil may be used to treat androgenic alopecia and is mildly effective when applied to the scalp twice daily. Only the 2% formulation is FDA approved for women.

B. Medications

Oral contraceptives are warranted as an initial therapy for women with hirsutism who are not actively pursuing pregnancy. To reduce the risk of deep venous thrombosis, an oral contraceptive is recommended with a low-dose of estradiol (20 mcg) and a progestin having a relatively low risk of venous thrombosis (norethindrone, norgestimate, levonorgestrel). A favored formulation for daily use contains norethindrone 1 mg with ethynodiol diacetate 20 mcg. Nevertheless, such oral contraceptives confer over twofold increased risk of deep venous thrombosis. Also, levonorgestrel causes insulin resistance, so its use is problematic in women with polycystic ovary syndrome. Oral contraceptives that contain particularly antiandrogenic progestins such as desogestrel (Azurette, Kariva), drospirenone (Yaz, Gianvi), norgestimate (Ortho Tri-Cyclen Lo), or cyproterone acetate (Diane 35, not available in United States) more effectively reduce hirsutism and acne; however, such antiandrogenic oral contraceptives confer a fourfold risk of deep venous thrombosis, and their use is discouraged in high-risk patients.

Cyproterone acetate is a unique progestin that is used to treat women with hirsutism worldwide, except in the United States, where it is not FDA-approved. Cyproterone acetate blocks androgen receptors as well as 5-alpha-reductase activity while also suppressing testosterone levels. It is typically prescribed as an oral contraceptive in a dose of 2 mg with ethynodiol diacetate 35 mcg.

Combined oral contraceptives are relatively contraindicated for women who are predisposed to thromboembolism, such as women who are smokers or who have migraines, women who are over age 39 years or who are obese, those with hypertension or a personal history of thromboembolism. Metabolic syndrome and hypertriglyceridemia are seen, particularly with antiandrogenic progestins.

Spironolactone is effective for reducing hirsutism, acne, and androgenic alopecia in women and is a first-line medical strategy for these women. It may be taken in doses

of 100–200 mg orally daily (taken as a single dose or in two divided doses) on days 5–25 of the menstrual cycle or daily if used concomitantly with an oral contraceptive. Spironolactone is contraindicated in pregnancy, so reproductive-age women must use reliable contraception during this therapy. Hyperkalemia is an uncommon side effect, but serum potassium should be checked 1 month after beginning therapy or after dosage increases. Spironolactone should be avoided or used cautiously in women with kidney disease or who are taking an ACE inhibitor or ARB. Spironolactone should not be given with an oral contraceptive containing drospirenone because the progestin has an anti-mineralocorticoid effect that predisposes to hyperkalemia. Trimethoprim-sulfamethoxazole should not be taken along with high-dose spironolactone. Trimethoprim has potassium-sparing diuretic effects and combining it with spironolactone increases the risk of severe hyperkalemia and sudden death. Side effects of spironolactone include breast tenderness, menstrual irregularity, headaches, nausea, and fatigue, which may improve with continued treatment or dose reduction; paradoxical scalp hair loss has been reported at higher doses.

Flutamide and **bicalutamide** inhibit testosterone binding to androgen receptors and also suppress serum testosterone. These drugs can rarely cause severe hepatotoxicity and exposure during pregnancy causes fetal malformations. Therefore, the use of these drugs for hirsutism is discouraged. They should only be used as a last resort for women with severe hirsutism/virilization and only with strict contraceptive precautions and very close monitoring for hepatic toxicity. Flutamide is given orally in a dosage of 250 mg twice daily for the first year and then 125–250 mg/day for maintenance. Flutamide decreases cortisol renal clearance and corticosteroid replacement doses (eg, in congenital adrenal hyperplasia) should be reduced when flutamide is added. Bicalutamide is given in a dosage of 50 mg once daily.

Finasteride inhibits 5-alpha-reductase, the enzyme that converts testosterone to active dihydrotestosterone in the skin. It provides inconsistent reduction in hirsutism and androgenic alopecia over 6 months. Also, this drug causes pseudohermaphroditism in male infants if mistakenly taken during pregnancy. Therefore, the use of finasteride for hirsutism is strongly discouraged.

Metformin alone is ineffective in improving hirsutism, but can enhance the anti-hirsutism effect of spironolactone. Start metformin at a dose of 500 mg/day with breakfast for 1 week, then increased to 500 mg with breakfast and dinner. If this dose is clinically insufficient but tolerated, the dose may be increased to 850–1000 mg twice daily with meals. The most common side effects are dose-related gastrointestinal upset and diarrhea or constipation. Metformin appears to be nonteratogenic. Although metformin reduces insulin resistance, it does not cause hypoglycemia in nondiabetic patients. Metformin is contraindicated in severe kidney or liver disease. **GLP-1 agonist** therapy reduced weight and serum testosterone levels in women with PCOS in one short-term study. However, an effect on hirsutism has not been demonstrated clinically.

Simvastatin can reduce hirsutism in women with PCOS. In one study, simvastatin 20 mg orally daily was given to women receiving an oral contraceptive for PCOS. Besides improving their serum lipid profiles, women receiving simvastatin had greater decreases in hirsutism and serum free testosterone levels than the women receiving an oral contraceptive alone. Atorvastatin also reduced serum testosterone by an average of 25% in women with PCOS.

Glucocorticoid replacement is necessary for women with classical congenital adrenal hyperplasia (21-hydroxylase deficiency) with hirsutism and adrenal insufficiency that requires glucocorticoid and mineralocorticoid replacement. However, women with partial “late-onset” 21-hydroxylase deficiency are not cortisol deficient and do not require glucocorticoid replacement. Also, glucocorticoids are ineffective in reducing hirsutism in these women. However, such women may require replacement doses of glucocorticoids (prednisone, methylprednisolone) to normalize menses and for ovulation induction. However, long-term administration of supraphysiologic doses of glucocorticoids should be avoided.

GnRH agonist therapy has been successful in treating postmenopausal women with severe ovarian hyperandrogenism when laparoscopic oophorectomy is contraindicated or declined by the patient.

C. Surgery

Androgenizing tumors of the adrenal or ovary are resected laparoscopically. Postmenopausal women with severe hyperandrogenism should undergo laparoscopic bilateral oophorectomy (if CT scan of the adrenals and ovaries is normal), since small hilar cell tumors of the ovary may not be visible on scans. Women with classic salt-wasting congenital adrenal hyperplasia and infertility or treatment-resistant hyperandrogenism may be treated with laparoscopic bilateral adrenalectomy.

Barrios P et al. Treatment options for hirsutism: a systematic review and network meta-analysis. *J Clin Endocrinol Metab*. 2018;103:1258. [PMID: 29522176]

Fraison E et al. Metformin versus the combined oral contraceptive pill for hirsutism, acne and menstrual pattern in polycystic ovary syndrome. *Cochrane Database Syst Rev*. 2020;8:CD005552. [PMID: 32794179]

Martin KA et al. Evaluation and treatment of hirsutism in premenopausal women: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2018;103:1233. [PMID: 29522147]

AMENORRHEA & MENOPAUSE

PRIMARY AMENORRHEA

Menarche ordinarily occurs between ages 11 and 15 years (average in the United States: 12.7 years) (see also Chapter 18). The failure of any menses to appear is termed “primary amenorrhea,” and evaluation is commenced either (1) at age 14 years if neither menarche nor any breast development has occurred or if height is in the lowest 3% for ethnicity, or (2) at age 16 years if menarche has not occurred.

Etiology of Primary Amenorrhea

The etiologies for primary amenorrhea include hypothalamic-pituitary causes, hyperandrogenism, ovarian causes (gonadal dysgenesis, Müllerian dysgenesis), disorders of sexual development (pseudohermaphroditism), uterine causes, and pregnancy.

A. Hypothalamic-Pituitary Causes (With Low or Normal FSH)

The most common cause of primary amenorrhea is a variant of normal known as constitutional delay of growth and puberty, which accounts for about 30% of delayed puberty cases. There is a strong genetic basis for this condition; over 50% of girls with it have a family history of delayed puberty. However, constitutional delay of growth and puberty is a diagnosis of exclusion.

A genetic deficiency of GnRH and gonadotropins may be isolated or associated with other pituitary deficiencies or diminished olfaction (Kallmann syndrome). Hypothalamic lesions, particularly craniopharyngioma, may be present. Pituitary tumors may be nonsecreting or may secrete PRL or GH. Cushing syndrome may be caused by corticosteroid treatment, a cortisol-secreting adrenal tumor, or an ACTH-secreting pituitary tumor. Hypothyroidism can delay adolescence. Head trauma or encephalitis can cause gonadotropin deficiency. Primary amenorrhea may also be caused by severe illness, vigorous exercise (eg, ballet dancing, running), stressful life events, dieting, or anorexia nervosa; however, these conditions should not be assumed to account for amenorrhea without a full endocrinologic evaluation.

B. Uterine Causes (With Normal FSH)

Müllerian agenesis (Mayer-Rokitansky-Küster-Hauser syndrome) results in a missing uterus and variable degrees of upper vaginal hypoplasia. It is the most common cause of permanent primary amenorrhea. Affected women have intact ovaries and undergo an otherwise normal puberty.

An imperforate hymen is occasionally the reason for the absence of visible menses.

C. Ovarian Causes (With High FSH)

Gonadal dysgenesis (Turner syndrome and variants) is a frequent cause of primary amenorrhea. Autoimmune ovarian failure is another cause. Rare deficiencies in certain ovarian steroidogenic enzymes are causes of primary hypogonadism without virilization: 3-beta-hydroxysteroid dehydrogenase deficiency (adrenal insufficiency with low serum 17-hydroxyprogesterone) and P450c17 deficiency (hypertension and hypokalemia with high serum 17-hydroxyprogesterone).

D. Hyperandrogenism (With Low or Normal FSH)

Polycystic ovaries and ovarian tumors can secrete excessive testosterone. Excess testosterone can also be secreted by adrenal tumors or by adrenal hyperplasia caused by steroidogenic enzyme defects such as P450c21 deficiency (salt-wasting) or P450c11 deficiency (hypertension). Androgenic steroid abuse may also cause this syndrome.

E. 46,XY Disorders of Sexual Development (Pseudohermaphroditism)

Complete androgen insensitivity syndrome is caused by homozygous inactivating mutations in the androgen receptor. 46,XY individuals with complete androgen insensitivity syndrome are born with normal external female genitalia, although some may have labial or inguinal swellings due to cryptorchid testes. Affected individuals are phenotypic girls and experience normal breast development at puberty, but fail to develop sexual hair and have primary amenorrhea.

Partial androgen insensitivity syndrome in 46,XY individuals results in variable degrees of ambiguous genitalia.

F. Pregnancy (With High hCG)

Pregnancy may be the cause of primary amenorrhea even when the patient refutes having had sexual intercourse.

► Clinical Findings

A. Symptoms and Signs

Headaches or visual field abnormalities implicate a hypothalamic or pituitary tumor. Signs of pregnancy may be present. Blood pressure elevation, acne, and hirsutism should be noted. Short stature may be seen with an associated GH or thyroid hormone deficiency. Short stature with manifestations of gonadal dysgenesis indicates Turner syndrome. Olfactory deficits are seen in Kallmann syndrome. Obesity and short stature may be signs of Cushing syndrome. Tall stature may be due to eunuchoidism or acromegaly. Hirsutism or virilization suggests excessive testosterone.

An external pelvic examination plus a rectal examination should be performed to assess hymen patency and the presence of a uterus.

B. Laboratory and Radiologic Findings

The initial endocrine evaluation should include serum FSH, LH, PRL, total and free testosterone, TSH, FT₄, and beta-hCG (pregnancy test). Patients who are virilized or hypertensive require serum electrolyte determinations and further hormonal evaluation (see Hirsutism & Virilization, above). MRI of the hypothalamus and pituitary is used to evaluate teens with primary amenorrhea and low or normal FSH and LH—especially those with high PRL levels. Pelvic duplex/color sonography is very useful. Girls who have a normal uterus and high FSH without the classic features of Turner syndrome may require a karyotype to diagnose X chromosome mosaicism.

► Treatment

Treatment of primary amenorrhea is directed at the underlying cause. Girls with permanent hypogonadism are treated with HRT.

Committee on Adolescent Health Care. ACOG committee opinion no. 728: Müllerian agenesis: diagnosis, management, and treatment. *Obstet Gynecol*. 2018;131:e35. [PMID: 29266078]

Varughese R et al. Fifteen-minute consultation: a structured approach to the child with primary amenorrhea. *Arch Dis Child Educ Pract Ed*. 2021;106:18. [PMID: 32561551]

SECONDARY AMENORRHEA

► General Considerations

Secondary amenorrhea is defined as the absence of menses for 3 consecutive months in women who have passed menarche. Menopause is defined as the terminal episode of naturally occurring menses; it is a retrospective diagnosis, usually made after 12 months of amenorrhea.

► Etiology & Clinical Findings

The causes of secondary amenorrhea include pregnancy, hypothalamic-pituitary causes, hyperandrogenism, uterine causes, premature ovarian failure, and menopause.

A. Pregnancy (High hCG)

Pregnancy is the most common cause for secondary amenorrhea in premenopausal women. The differential diagnosis includes rare ectopic secretion of hCG by a choriocarcinoma or bronchogenic carcinoma.

B. Hypothalamic-Pituitary Causes (With Low or Normal FSH)

The hypothalamus must release GnRH in a pulsatile manner for the pituitary to secrete gonadotropins. GnRH pulses occurring more than once per hour favor LH secretion, while less frequent pulses favor FSH secretion. In normal ovulatory cycles, GnRH pulses in the follicular phase are rapid and favor LH synthesis and ovulation; ovarian luteal progesterone is then secreted that slows GnRH pulses, causing FSH secretion during the luteal phase. Most women with hypothalamic amenorrhea have a persistently low frequency of GnRH pulses.

Secondary “hypothalamic” amenorrhea may be caused by stressful life events such as school examinations or leaving home. Such women usually have a history of normal sexual development and irregular menses since menarche. Amenorrhea may also be the result of strict dieting, vigorous exercise, organic illness, or anorexia nervosa. Intrathecal infusion of opioids causes amenorrhea in most women. These conditions should not be assumed to account for amenorrhea without a full physical and endocrinologic evaluation. Young women in whom the results of evaluation and progestin withdrawal test are normal have noncyclic secretion of gonadotropins resulting in anovulation. Such women typically recover spontaneously but should have regular evaluations and a progestin withdrawal test about every 3 months to detect loss of estrogen effect.

PRL elevation may cause amenorrhea. Pituitary tumors or other lesions may cause hypopituitarism. Corticosteroid excess suppresses gonadotropins.

C. Hyperandrogenism (With Low-Normal FSH)

Elevated serum levels of testosterone can cause hirsutism, virilization, and amenorrhea. In PCOS, GnRH pulses are persistently rapid, favoring LH synthesis with excessive androgen secretion; reduced FSH secretion impairs follicular maturation. Progesterone administration can slow the GnRH pulses, thus favoring FSH secretion that induces follicular maturation. Rare causes of secondary amenorrhea include adrenal P450c21 deficiency, ovarian or adrenal malignancies, and Cushing syndrome. Anabolic steroids also cause amenorrhea.

D. Uterine Causes (With Normal FSH)

Infection of the uterus commonly occurs following delivery or D&C but may occur spontaneously. Endometritis due to tuberculosis or schistosomiasis should be suspected in endemic areas. Endometrial scarring may result, causing amenorrhea (Asherman syndrome). Such women typically continue to have monthly premenstrual symptoms. The vaginal estrogen effect is normal.

E. Menopause (With High FSH)

Early menopause refers to primary ovarian failure that occurs before age 45. It affects approximately 5% of women. About 1% of women experience **premature menopause** that is defined as ovarian failure before age 40; about 30% of such cases are due to autoimmunity against the ovary. X chromosome mosaicism accounts for 8% of cases of premature menopause. Other causes include surgical bilateral oophorectomy, radiation therapy for pelvic malignancy, and chemotherapy. Women who have undergone hysterectomy are prone to premature ovarian failure even though the ovaries were left intact. Myotonic dystrophy, galactosemia, and mumps oophoritis are additional causes. Early or premature menopause is frequently familial. Ovarian failure is usually irreversible. Women with premature menopause, compared to women with normal menopause, have a 50% increased risk of coronary disease, a 23% increased risk of stroke, and a 12% increased overall mortality.

Laboratory findings in premature menopause—An elevated hCG overwhelmingly indicates pregnancy; false-positive testing may occur very rarely with ectopic hCG secretion (eg, choriocarcinoma or bronchogenic carcinoma). Further laboratory evaluation for women who are not pregnant includes serum PRL, FSH and LH (both elevated in menopause), and TSH. Hyperprolactinemia or hypopituitarism (without obvious cause) should prompt an MRI study of the pituitary region. Routine testing of kidney and liver function (BUN, serum creatinine, bilirubin, alkaline phosphatase, and alanine aminotransferase) is also performed. A serum testosterone level is obtained in hirsute or virilized women.

Treatment

Nonpregnant women without any laboratory abnormality may receive a 10-day course of a progestin (eg, medroxyprogesterone acetate, 10 mg/day); absence of withdrawal

menses typically indicates a lack of estrogen or a uterine abnormality. (See Treatment section of Normal Menopause, below.)

Committee on Gynecologic Practice. Committee Opinion No. 698: Hormone therapy in primary ovarian insufficiency. Obstet Gynecol. 2017;129:e134. [PMID: 28426619]

Gordon CM et al. Functional hypothalamic amenorrhea: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2017;102:1413. [PMID: 28368518]

NORMAL MENOPAUSE



ESSENTIALS OF DIAGNOSIS

- ▶ Menopause is a retrospective diagnosis after 12 months of amenorrhea.
- ▶ Approximately 80% of women experience hot flushes and night sweats.
- ▶ High FSH and low estradiol help confirm the diagnosis.

General Considerations

Normal menopause refers to primary ovarian failure that occurs after age 45. “Climacteric” is defined as the period of natural physiologic decline in ovarian function, generally occurring over about 10 years. By about age 40 years, the remaining ovarian follicles are those that are the least sensitive to gonadotropins. Increasing titers of FSH are required to stimulate estradiol secretion. Estradiol levels may actually rise during early climacteric.

The normal age for menopause in the United States ranges between 48 and 55 years, with an average of about 51.5 years. Serum estradiol levels fall and the remaining estrogen after menopause is estrone, derived mainly from peripheral aromatization of adrenal androstenedione. Such peripheral production of estrone is enhanced by obesity and liver disease. Individual differences in estrone levels partly explain why the symptoms noted above may be minimal in some women but severe in others.

Clinical Findings

A. Symptoms and Signs

1. Cessation of menstruation—Menstrual cycles generally become irregular as menopause approaches. Anovulatory cycles occur more often, with irregular cycle length and occasional menorrhagia. Menstrual flow usually diminishes in amount owing to decreased estrogen secretion, resulting in less abundant endometrial growth. Finally, cycles become longer, with missed periods or episodes of spotting only. When no bleeding has occurred for 1 year, the menopausal transition can be said to have occurred. Any bleeding after 6 months from the cessation of menses warrants investigation by endometrial curettage or aspiration to rule out endometrial cancer.

2. Vasomotor symptoms—Hot flushes (feelings of intense heat over the trunk and face, with flushing of the skin and sweating) occur in over 80% of women as a result of the decrease in ovarian hormones. Hot flushes can begin before the cessation of menses. Menopausal vasomotor symptoms last longer than previously thought, and there are ethnic differences in the duration of symptoms. Vasomotor symptoms last more than 7 years in more than 50% of the women. African-American women report the longest duration of vasomotor symptoms. Hot flushes occur more frequently at night, causing sweating and insomnia that result in fatigue on the following day.

3. Genitourinary syndrome of menopause (GSM)

Decreased estrogen secretion results in less vaginal lubrication and vulvovaginal atrophy with dryness, dyspareunia, burning, and pruritus. Estrogen deficiency also causes urinary frequency, urgency, dysuria, and an increased risk of urinary tract infections. GSM does not tend to improve over time, in contrast to menopausal hot flushes. Pelvic examination reveals pale, smooth vaginal mucosa and a small cervix and uterus. The ovaries are not normally palpable after menopause.

4. Other menopausal manifestations—Over 60% of women experience cognitive problems, particularly during the menopausal transition. Most commonly, perimenopausal women complain of difficulty retrieving words and short-term forgetfulness (such as not remembering why they entered a room or misplacing keys or glasses). There is an increased incidence of sleep disturbance and mood changes. Postmenopausal osteoporosis presents later in menopause with fragility fractures of long bones and vertebrae.

B. Laboratory Findings

No laboratory testing is required to diagnose normal menopause when amenorrhea occurs at the expected age. The expected age of menopause correlates with a woman's mother's age at menopause and varies among different kindreds and ethnic groups. An elevated serum FSH with a low or low-normal serum estradiol helps confirm the diagnosis. A vaginal cytologic examination will show a low estrogen effect with predominantly parabasal cells, indicating lack of epithelial maturation due to hypoestrogenism.

Treatment

A. Non-Estrogen Treatments

Women with night sweats should sleep in a cool room and avoid the use of down comforters. Eliminating triggers for hot flushes, such as smoking, alcohol, caffeine, and hot spicy foods, may be helpful. Slow, deep breathing can ameliorate hot flushes. **Aerobic training** for 50 minutes four times weekly reduced all menopausal symptoms except vaginal dryness in a randomized controlled trial. **Clinical hypnosis** reduced hot flushes over 12 weeks in one study. Acupuncture may help alleviate symptoms in some women. Vaginal lubricants can be used daily or 2 hours before intercourse.

For women with severe hot flushes who cannot take estrogen, SSRIs may offer modest relief effective within a week; escitalopram (10–20 mg orally daily) or paroxetine (7.5 mg orally daily) can reduce hot flushes significantly, but they must not be used by women taking tamoxifen, since SSRIs inhibit the conversion of tamoxifen to its active metabolite. Venlafaxine extended release (75 mg orally daily) may also be effective and does not have a drug interaction with tamoxifen. Sexual dysfunction has not been as significant with the latter drugs when used for vasomotor symptoms, compared to their use for depression. Gabapentin is also effective in oral doses titrated up to 200–800 mg every 8 hours. Side effects such as drowsiness, dizziness, and headache, which are most pronounced during the first 2 weeks of therapy, often improve within 4 weeks. An herb, black cohosh, may possibly relieve hot flushes. Tamoxifen and raloxifene offer bone protection but aggravate hot flushes. Women with low serum testosterone levels may experience hypoactive sexual desire disorder that may respond to low-dose testosterone replacement.

B. Estrogen Replacement Therapy—Benefits

Estrogen replacement therapy (ERT) improves overall survival for women who begin ERT before age 60 or within 10 years of menopause. In the California Teachers Study, ERT in such women was associated with a dramatic 46% reduction in all-cause mortality, particularly cardiovascular disease. Also, a 20-year study of 8801 women living in a retirement community found that ERT was associated with improved survival. Age-adjusted mortality rates were 56.4 (per 1000 person-years) among nonusers and 50.4 among women who had used estrogen for 15 years or longer. The reduction in cardiovascular disease among younger postmenopausal women taking ERT may be explained by the reduction in serum levels of atherogenic lipoprotein(a) with ERT, with or without a progestin. Improvement in serum HDL cholesterol is greatest with unopposed estrogen but is also seen with the addition of a progestin. The survival advantage diminishes with age; no reduction in mortality was noted in the group of women aged 85–94 years. Nevertheless, other benefits are reasons to continue ERT beyond the first 10 years of menopause.

Other benefits of even low-dose ERT include the improvement in hot flushes and the prevention of postmenopausal osteoporosis and a 33% reduction in hip fractures. The WHI study found that women who received ERT experienced six fewer fractures/year per 10,000 women compared with placebo. ERT improves vaginal moisture and enhances libido in some women. ERT may also improve sleep disturbances and mild cognitive dysfunction, which are common menopausal symptoms. Unopposed estrogen improves perimenopause-related depression, but the addition of a progestin may negate this effect. Estrogen replacement may also help the joint pains, generalized body pain, and reduced physical function experienced by some women at the time of menopause. ERT also increases facial skin moisture and thickness and reduces seborrhea but does not prevent skin wrinkling.

Low-dose estrogen alone appears to have a negligible effect on breast cancer risk, with studies variably finding a decreased risk (Women's Health Initiative, WHI) or an increased risk of breast cancer (California Teachers' Study). However, combined daily estrogen and progestin increases the long-term risk for breast cancer. Transdermal estradiol replacement does not increase the risk of thromboembolic disease or stroke, whereas oral estrogens increase such risk.

In light of these considerations, estrogen replacement is most commonly prescribed for women in early menopause, when symptoms are worst and the benefits are greatest. Transdermal estrogen is favored over oral therapy to reduce the risk of thromboembolism. In women with an intact uterus, estrogen replacement without a progestin risks endometrial hypertrophy and dysfunctional uterine bleeding. The addition of a progestin, however, increases the risk of breast cancer. Therefore, only the smallest effective dose of estrogen should be used to avoid the need for progestins or use them in lower doses or intermittently. Also, progestin may be delivered directly to the uterus with progesterone-eluting intrauterine devices. The prescription of estrogen replacement to women up to 65 years of age is generally accepted. The American College of Obstetricians and Gynecologists and the North American Menopause Society have recommended that the decision to continue estrogen replacement past aged 65 should include an assessment of risks and benefits, particularly including relief from hot flushes, prevention of osteoporosis, and improved quality of life.

C. Estrogen Replacement Therapy—Risks

Oral ERT increases the risk of arterial and venous thrombotic events in a dose-dependent manner, although the absolute risk is small. The WHI study found that women who received long-term conventional oral combined HRT had an increased risk of deep venous thrombosis (3.5 per 1000 person-years) compared with women receiving placebo (1.7 per 1000 person-years). Oral estrogen also increases the risk of ischemic stroke by about 30%. Oral estrogen causes a particularly increased risk for thromboembolic disease among older women and those with increased stroke proclivity (current smokers and those with hypertension, atrial fibrillation, prior thromboembolic event). Long-term use of oral conjugated estrogens in women over age 65 has been associated with poorer cognitive performance, perhaps due to small strokes. Transdermal or vaginal estrogen administration avoids this risk. Urinary stress incontinence appears to be increased by conventional-dose oral estrogen replacement, whereas topical vaginal estrogen may have a beneficial effect. Estrogen replacement may cause mastalgia that typically responds to dose reduction. Estrogen replacement also appears to increase the risk of seizures in women with epilepsy. ERT can stimulate the growth of untreated large pituitary prolactinomas. Oral estrogens and SERMs also increase the risk of gastroesophageal reflux disease. Oral ERT can increase the size of hepatic hemangiomas, but significant enlargement is uncommon. Conventional doses of ERT carry higher risks than lower doses. The risks for ERT also depend on whether estrogen is administered alone (unopposed ERT) or with a progestin (combined ERT).

1. Risks of ERT without progestin (unopposed ERT)—The California Teachers' Study reported an *increased breast cancer risk* among such women while the WHI study reported that postmenopausal women taking unopposed estrogen had a *reduced breast cancer risk*. Women taking lower-dose unopposed estrogen therapy are expected to have a lower long-term risk of breast cancer compared to women taking high-dose estrogens.

Conventional-dose unopposed conjugated estrogen replacement (0.625–1.25 mg daily) increases the risk of endometrial hyperplasia and dysfunctional uterine bleeding, which often prompts patients to stop the estrogen. However, lower-dose unopposed estrogen confers a much lower risk of dysfunctional uterine bleeding. Recurrent dysfunctional bleeding necessitates a pelvic examination and possibly an endometrial biopsy. There has been considerable concern that unopposed estrogen replacement might increase the risk for endometrial carcinoma. However, a Cochrane Database Review found no increased risk of endometrial carcinoma in a review of 30 randomized controlled trials. Therefore, lower-dose unopposed estrogen replacement does not appear to confer any significant increased risk for endometrial cancer.

The risk of stroke among women taking a conventional dose of unopposed estrogen is increased; the risk is about 44 strokes per 10,000 person-years versus about 32 per 10,000 person-years in women taking placebo. However, transdermal or transvaginal ERT does not appear to increase the risk of stroke.

Oral estrogens can cause hypertriglyceridemia, particularly in women with preexisting hyperlipidemia, rarely resulting in pancreatitis. Postmenopausal estrogen therapy also slightly increases the risk of gallstones and cholecystitis. These side effects may be reduced or avoided by using transdermal or vaginal estrogen replacement.

2. Risks of ERT with a progestin (combined ERT)—Long-term conventional-dose oral combined HRT increases breast density and the risk for abnormal mammograms (9.4% versus 5.4% for placebo). There is also a higher risk of breast cancer (8 cases per 10,000 women/year versus 6.5 cases per 10,000 women/year for placebo). The implicated progestins have been medroxyprogesterone acetate and norethisterone, so prescribing has shifted to bio-identical progesterone. The increased risk of breast cancer is highest shortly after menopause (about 2 cases per 1000 women annually). This increased risk for breast cancer appears to mostly affect relatively thin women with a BMI less than 24.4. The Iowa Women's Health Study reported an increase in breast cancer with HRT only in women consuming more than 1 oz of alcohol weekly. No accelerated risk of breast cancer has been seen in users of HRT who have benign breast disease or a family history of breast cancer. Women in whom new-onset breast tenderness develops with combined HRT have an increased risk of breast cancer, compared with women without breast tenderness. Women receiving combined HRT experience no increased overall mortality and no increased overall or specific cancer mortality.

The Women's Health Initiative Mental Study (WHIMS) followed the effect of combined conventional-dose oral HRT on cognitive function in women 65–79 years old.

HRT did not protect these older women from cognitive decline. In fact, they experienced an increased risk for severe dementia at a rate of 23 more cases/year for every 10,000 women over age 65 years. It is unknown whether this finding applies to younger postmenopausal women.

In the WHI study, women receiving conventional-dose combined oral HRT experienced an increased risk of stroke (31 strokes per 10,000 women/year versus 26 strokes per 10,000 women/year for placebo). Stroke risk was also increased by hypertension, diabetes, and smoking.

Women taking combined oral estrogen–progestin replacement do not experience an increased risk of ovarian cancer. They do experience a slightly increased risk of developing asthma.

Progestins may cause moodiness, particularly in women with a history of premenstrual dysphoric disorder. Cycled progestins may trigger migraines in certain women. Many other adverse reactions have been reported, including breast tenderness, alopecia, and fluid retention. Contraindications to the use of progestins include thromboembolic disorders, liver disease, breast cancer, and pregnancy.

D. Hormone Replacement Therapy Agents

Hormone replacement needs to be individualized. Ideally, in women with an intact uterus, very low-dose transdermal estradiol may be used alone or with intermittent progestin or a progesterone-eluting intrauterine device, in order to reduce the risk of endometrial hyperplasia, while avoiding the need for daily oral progestin. Vaginal estrogen can be added if low-dose systemic estradiol replacement is insufficient to relieve symptoms of vulvovaginal atrophy. Women who have had a hysterectomy may receive transdermal estrogen at whatever is the lowest dose that adequately relieves symptoms. However, some women cannot find sufficient relief with transdermal estradiol and must use an oral preparation.

1. Transdermal estradiol—Estradiol can be delivered systemically with different systems of skin patches, mists, or gels. Transdermal estradiol works for most women, but some women have poor transdermal absorption. If a woman has a skin reaction to an estradiol patch, then a gel or mist may be tried at different doses until the ideal formulation is found.

A. ESTRADIOL PATCHES MIXED WITH ADHESIVE—These systems tend to cause minimal skin irritation. Generic estradiol transdermal is available as a patch that is replaced biweekly (0.025, 0.0375, 0.05, 0.075, 0.1 mg/day) or weekly (0.025, 0.0375, 0.05, 0.06, 0.075, 0.1 mg/day). Brand products include: Vivelle-Dot (0.025 mg/day) or Minivivelle (0.0375, 0.05, 0.075, or 0.1 mg/day) or Alora (0.025, 0.05, 0.075, or 0.1 mg/day), replaced twice weekly; Climara (0.025, 0.0375, 0.05, 0.06, 0.075, or 0.1 mg/day), replaced weekly; and Menostar (0.014 mg/day), replaced weekly. This type of estradiol skin patch can be cut in half and applied to the skin without proportionately greater loss of potency. Minivivelle patches are the smallest.

B. ESTRADIOL MISTS, GELS AND LOTION—Evamist is a topical mist dispenser that dispenses 1.53 mg estradiol/spray; 1–3 sprays are applied to the inner forearm daily; a

single daily spray may provide sufficiently low-dose estradiol to possibly obviate the need for daily progestin in women with an intact uterus. EstroGel 0.06% in a metered-dose pump dispenses 0.75 mg estradiol per actuation (dose: half to 2 actuations/day). Elestrin 0.06% in a metered-dose pump dispenses 0.52 mg estradiol per activation (dose: half to 2 actuations/day). These gels are applied daily to one arm from the wrist to the shoulder after bathing. Divigel 0.1% gel (0.25, 0.5, 0.75 1 g/packet) is applied to the upper-inner thigh or inner arm daily. Estrisorb 2.5% is available in 1.74-g pouches (4.35 mg estradiol); 1–2 pouches of lotion are applied to the thigh/calf daily. To avoid spreading topical estradiol to others, the hands should be washed and precautions taken to avoid prolonged skin contact with children. Application of sunscreen prior to estradiol gel has been reported to increase the transdermal absorption of estradiol.

C. ESTRADIOL PATCHES WITH PROGESTIN MIXED WITH ADHESIVE—These preparations mix estradiol with either norethindrone acetate or levonorgestrel. Combipatch (0.05 mg E with 0.14 mg norethindrone acetate daily or 0.05 mg E with 0.25 mg norethindrone acetate daily) is replaced twice weekly. Climara Pro (0.045 mg E with 0.015 mg levonorgestrel daily) is replaced once weekly. The addition of a progestin reduces the risk of endometrial hyperplasia, but breakthrough bleeding occurs commonly. The combined patch increases the risk of breast cancer. Scalp hair loss, acne, weight gain, skin reactions, and poor skin adherence have been reported with these patches.

2. Oral estrogen

A. ORAL ESTROGEN-ONLY PREPARATIONS—These preparations include conjugated equine estrogens that are available as Premarin (0.3, 0.45, 0.625, 0.9, and 1.25 mg), conjugated plant-derived estrogens (eg, Menest, 0.3, 0.625, and 2.5 mg), and conjugated synthetic estrogens (Cenestin) (0.3, 0.45, 0.625, 0.9, and 1.25 mg) and Enjuvia (0.3, 0.45, 0.625, 0.9, and 1.25 mg). Other preparations include estradiol (0.5, 1, and 2 mg) and estropipate (0.75, 1.5, and 3 mg).

B. ORAL ESTROGEN PLUS PROGESTIN PREPARATIONS—Conjugated equine estrogens with medroxyprogesterone acetate are available as Prempro (0.3/1.5, 0.45/1.5, 0.625/2.5, and 0.625 mg/5 mg); conjugated equine estrogens for 14 days cycled with conjugated equine estrogens plus medroxyprogesterone acetate for 14 days are available as Premphase (0.625/0, then 0.625 mg/5 mg); estradiol with norethindrone acetate (0.5/0.1 and 1 mg/0.5 mg); ethinyl estradiol with norethindrone acetate is available as Femhrt (2.5/0.5 and 5 mcg/1 mg) and Jinteli (5 mcg/1 mg); estradiol with drospirenone is available as Angeliq (0.5 mg/0.25 mg, and 1.0 mg/0.5 mg); estradiol with norgestimate is available as Prefest (estradiol 1 mg/day for 3 days, alternating with 1 mg estradiol/0.09 mg norgestimate daily for 3 days); estradiol with progesterone is available as Bijuva (1 mg/100 mg) capsules. Oral contraceptives can also be used for combined HRT.

3. Vaginal estrogen—Vaginal estrogen is intended to deliver estrogen directly to local tissues and is moderately effective in reducing symptoms of urogenital atrophy, while minimizing systemic estrogen exposure. Some

estrogen is absorbed systemically and can relieve menopausal symptoms. Vaginal estrogen can be used without a break at low doses or in women who have had a hysterectomy. To reduce the risk of endometrial proliferation and dysfunctional bleeding, manufacturers recommend that these preparations be used for only 3–6 months and for only 3 out of every 4 weeks in women with an intact uterus, since vaginal estrogen can cause endometrial proliferation. However, most clinicians use them for longer periods and without cycling. Vaginal estrogen can be administered in three different ways: creams, tablets, and rings.

A. ESTROGEN VAGINAL CREAMS—These creams are administered intravaginally with a measured-dose applicator daily for 2 weeks for atrophic vaginitis, then administered one to three times weekly. *Conjugated equine estrogens* are available as Premarin Vaginal (0.625 mg/g cream), dosed as 0.25–2 g cream administered vaginally one to three times weekly. *Estradiol* is available as Estrace Vaginal (0.1 mg/g cream), 1 g cream administered vaginally one to two times weekly.

B. ESTRADIOL VAGINAL TABLETS AND SOFTGEL INSERTS—*Vagifem* and *Yuvafem* (generic equivalent) are available as 10 mcg tablets. *Invexxy* is a softgel vaginal insert (4 mcg or 10 mcg estradiol in a coconut oil base). Either preparation can be administered intravaginally daily for 2 weeks for atrophic vaginitis, then twice weekly. *Prasterone* (*Intrarosa*) is available as a 6.5 mg vaginal insert that is used daily. Vaginal preparations are usually inserted at bedtime.

C. ESTRADIOL VAGINAL RINGS—These rings are inserted manually into the upper third of the vagina, worn continuously, and replaced every 3 months. Only a small amount of the released estradiol enters the systemic circulation. Vaginal rings do not usually interfere with sexual intercourse. If a ring is removed or descends into the introitus, it may be washed in warm water and reinserted. *Estring* (2 mg estradiol/ring) releases 17-beta-estradiol 7.5 mcg/day with only 8% entering the systemic circulation, resulting in mean serum estradiol concentrations of only about 10 pg/mL; it is most effective for local vaginal symptoms. *Femring* releases estradiol acetate that is quickly hydrolyzed to estradiol and is available in two strengths: 12.4 mg/ring releases estradiol acetate 0.05 mg/day or 24.8 mg/ring releases estradiol acetate 0.1 mg/day, resulting in mean serum estradiol concentrations of about 40 pg/mL and 80 pg/mL, respectively; it is effective for both systemic and local vaginal symptoms. Both rings are replaced every 90 days. For women with postmenopausal urinary urgency and frequency, even the low-dose *Estring* can successfully reduce urinary symptoms and vaginal dryness.

D. ESTRADIOL WITH PROGESTIN VAGINAL RINGS—*Nuva Ring* releases a mixture of ethinyl estradiol 0.015 mg/day and etonogestrel 0.12 mg/day. It is a contraceptive vaginal ring that is placed in the vagina on or before day 5 of the menstrual cycle, left for 3 weeks, removed for 1 week, and then replaced.

4. Estradiol injections—Parenteral estradiol should be used only for particularly severe menopausal symptoms when other measures have failed or are contraindicated. Estradiol cypionate (Depo-Estradiol 5 mg/mL) may be administered

intramuscularly in doses of 1–5 mg every 3–4 weeks. Estradiol valerate (20 or 40 mg/mL) may be administered intramuscularly in doses of 10–20 mg every 4 weeks. Women with an intact uterus should receive progestin for the last 10 days of each cycle.

5. Oral progestins—For a woman with an intact uterus, long-term conventional-dose unopposed systemic estrogen therapy can cause endometrial hyperplasia, which typically results in dysfunctional uterine bleeding and might rarely lead to endometrial cancer. Progestin therapy transforms proliferative into secretory endometrium, causing a possible menses when given intermittently or no bleeding when given continuously.

The type of progestin preparation, its dosage, and the timing of administration may be tailored to the given situation. Progestins may be given daily, monthly, or at longer intervals. When given episodically, progestins are usually administered for 7- to 14-day periods. Bedtime administration may improve sleep. Some women find that progestins produce adverse effects, such as irritability, nausea, fatigue, or headache; long-term progestins given with estrogen replacement increase the risk for breast cancer.

Oral progestins are available in different formulations: Micronized progesterone (100 mg and 200 mg/capsule) may carry a reduced risk of breast cancer, vascular thromboembolism, and reduced adverse effects on mood and lipid levels compared to other progestins, according to observational studies. Other progestins include medroxyprogesterone (2.5, 5.0, and 10 mg/tablet), norethindrone acetate (5 mg/tablet), and norethindrone (0.35 mg/tablet). Topical progesterone (20–50 mg/day) may reduce hot flushes in women who are intolerant to oral HRT. It may be applied to the upper arms, thighs, or inner wrists daily. It may be compounded as micronized progesterone 250 mg/mL in a transdermal gel. Its effects upon the breast and endometrium are unknown. Progesterone is also available as vaginal gels (eg, *Prochieve*, 4% = 45 mg/applicatorful, and 8% = 90 mg/applicatorful) that are typically given for secondary amenorrhea and administered vaginally every other day for six doses.

6. Vaginal progesterone—Vaginal progesterone minimizes dysfunctional uterine bleeding while reducing systemic progesterone exposure. *Crinone* and *Prochieve* contain 4% and 8% gel with 45 mg and 90 mg per applicatorful, respectively. *Endometrin* comes as a 100 mg vaginal insert. Administered twice weekly with daily estrogen, most women experience no endometrial hypertrophy or dysfunctional uterine bleeding.

7. Progestin-releasing intrauterine devices—Intrauterine devices that release progestins can be useful for women receiving ERT, since they can reduce the incidence of dysfunctional uterine bleeding and endometrial carcinoma without exposing women to the significant risks of systemic progestins. The Mirena intrauterine device releases levonorgestrel and is inserted into the uterus by a clinician within 7 days of the onset of menses. It is equally effective at reducing endometrial hyperplasia as cycled medroxyprogesterone acetate and is associated with less hirsutism. It remains effective for up to 5 years. Parous women are

generally better able to tolerate the Mirena intrauterine device than nulliparous women.

8. Selective estrogen receptor modulators—SERMs (eg, raloxifene, ospemifene, tamoxifen) are an alternative to estrogen replacement for hypogonadal women at risk for osteoporosis who prefer not to take estrogens because of their contraindications (eg, breast or uterine cancer) or side effects (see Osteoporosis, above). Raloxifene (Evista) does not reduce hot flushes, vaginal dryness, skin wrinkling, or breast atrophy; it does not improve cognition. However, in doses of 60 mg/day orally, it inhibits bone loss without stimulating effects upon the breasts. In fact, it reduces the risk of invasive breast cancer by about 50%. Raloxifene does not stimulate the endometrium and actually reduces the risk of endometrial carcinoma, so concomitant progesterone therapy is not required. Raloxifene slightly increases the risk of venous thromboembolism (though less so than tamoxifen), so it should not be used by women at prolonged bed rest or otherwise prone to thrombosis. Ospemifene (Ospheva) is a SERM that has unique estrogen-like effects on the vaginal epithelium and is indicated for the treatment of postmenopausal dyspareunia when other therapies are ineffective. Given orally in doses of 60 mg/day, it commonly aggravates hot flushes but has an estrogenic effect upon bone and slows bone loss in menopause. It does not usually cause endometrial hypertrophy. Ospemifene has unknown long-term effects upon the breast.

Tibolone (Livial) is a SERM whose metabolites have mixed estrogenic, progestogenic, and weak androgenic activity. It is comparable to HRT for the treatment of climacteric-related complaints. It does not appear to significantly stimulate proliferation of breast or endometrial tissue. It depresses both serum triglycerides and HDL cholesterol. Long-term studies are lacking. It is not available in the United States.

9. Androgen replacement therapy in women—Measurements of total serum testosterone with chromatography and tandem mass spectrometry are accurate, whereas direct assays for serum total and free testosterone are very inaccurate in the normal female range. In premenopausal women, serum testosterone levels decline with age. Between 25 and 45 years of age, women's testosterone levels fall 50%. After natural menopause, the ovaries remain a significant source for testosterone and serum testosterone levels do not fall abruptly. In contrast, very low serum testosterone levels are found in women after bilateral oophorectomy, autoimmune ovarian failure, or adrenalectomy, and in hypopituitarism. Testosterone deficiency contributes to hot flushes, loss of sexual hair, muscle atrophy, osteoporosis, and diminished libido, also known as hypoactive sexual desire disorder (see Chapter 25). Selected women may be treated with low-dose testosterone that result in physiologic premenopausal serum testosterone levels. In women with hypoactive sexual desire disorder, low-dose testosterone therapy improves libido, sexual responsiveness, and orgasmic function. Methyltestosterone can be compounded into capsules and taken orally in doses of 1.25–2.5 mg daily. Testosterone can also be compounded as a cream containing 1 mg/mL, with 1 mL applied to the

abdomen daily. Methyltestosterone also is available combined with esterified estrogens: 1.25 mg methyltestosterone/0.626 mg esterified estrogens or 2.5 mg methyltestosterone/1.25 mg esterified estrogens. The latter formulations are convenient but carry the same disadvantages as oral estrogen—particularly an increased risk of thromboembolism.

Women receiving androgen therapy must be monitored for the appearance of any acne or hirsutism, and serum testosterone levels are determined periodically if women feel that they are benefitting and long-term testosterone therapy is instituted. Side effects of low-dose testosterone therapy are usually minimal but may include erythrocytosis, emotional changes, hirsutism, acne, an adverse effect on lipids, and potentiation of warfarin anticoagulation therapy. Low-dose testosterone therapy tends to reduce both triglyceride and HDL cholesterol levels. Hepatocellular neoplasms and peliosis hepatitis, rare complications of oral androgens at higher doses, have not been reported with oral methyltestosterone doses of 2.5 mg or less daily.

Vaginal androgen is an option for postmenopausal women who are experiencing vaginal dryness and reduced sexual satisfaction. It is also an option for women who cannot use systemic or vaginal estrogen due to breast cancer. Testosterone cream 150–300 mcg (formulated) is administered vaginally daily for 2 weeks and then three times weekly. It improves sexual satisfaction while reducing vaginal dryness and dyspareunia without increasing systemic estrogen or testosterone levels. Prasterone 0.5% vaginal (Intrarosa), a formulation of DHEA, is available as a 6.5 mg tablet that is inserted vaginally nightly at bedtime. It is indicated for relief of moderate to severe dyspareunia of menopause. However, it is contraindicated in women with breast cancer.

Caution: *Androgens should not be given to women with liver disease or during pregnancy or breastfeeding.* Testosterone replacement therapy for women should be used judiciously, since long-term prospective clinical trials are lacking. An analysis of the Nurses' Health Study found that women who had been taking conjugated equine estrogens plus methyltestosterone experienced an increased risk of breast cancer, so breast cancer screening is recommended.

E. Surgical Menopause

The abrupt hormonal decrease resulting from bilateral oophorectomy generally results in severe vasomotor symptoms and rapid onset of dyspareunia and osteoporosis unless treated. If not contraindicated, estrogen replacement is generally started immediately after surgery. Either transdermal estradiol or an oral estrogen may be used. (See above.) No progestin is required in women who have had a hysterectomy.

Anagostis P et al. Menopause symptom management in women with dyslipidemias: an EMAS clinical guide. *Maturitas*. 2020;135:82. [PMID: 32209279]

Chlebowski RT et al. Association of menopausal hormone therapy with breast cancer incidence and mortality during long-term follow-up of the Women's Health Initiative randomized controlled clinical trials. *JAMA*. 2020;324:369. [PMID: 32721007]

- Davis SR et al. Global consensus position statement on the use of testosterone therapy for women. *J Clin Endocrinol Metab.* 2019;104:4660. [PMID: 31498871]
- Greendale GA et al. The menopause transition and cognition. *JAMA.* 2020;325:149. [PMID: 32163094]
- Kingsberg SA et al. Clinical effects of early or surgical menopause. *Obstet Gynecol.* 2020;135:853. [PMID: 32168205]
- NAMS 2017 Hormone Therapy Position Statement Advisory Panel. The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause.* 2017;24:728. [PMID: 28650869]
- Pinkerton JV. Hormone therapy for postmenopausal women. *N Engl J Med.* 2020;382:446. [PMID: 31995690]

TURNER SYNDROME (Gonadal Dysgenesis)



ESSENTIALS OF DIAGNOSIS

- ▶ Short stature with normal GH levels.
- ▶ Primary amenorrhea or early ovarian failure.
- ▶ Epicanthal folds, webbed neck, short fourth metacarpals.
- ▶ Renal and cardiovascular anomalies.

Turner syndrome comprises a group of X chromosome disorders that are associated with spontaneous abortion, primary hypogonadism, short stature, and other phenotypic anomalies (Table 26–15). It affects 1–2% of fetuses, of which about 97% abort, accounting for about 10% of all spontaneous abortions. Nevertheless, it affects about 1 in every 2500 live female births. Patients with the classic syndrome (about 50% of cases) lack one of the two X chromosomes (45,XO karyotype). About 12% of patients harbor mosaicism for Y chromosome sequences. Other patients with Turner syndrome have X chromosome abnormalities, such as ring X or Xq (X/abnormal X) or X chromosome deletions affecting all or some somatic cells (mosaicism, XX/XO).

1. Classic Turner Syndrome (45,XO Gonadal Dysgenesis)

► Clinical Findings

A. Symptoms and Signs

Features of Turner syndrome are variable and may be subtle in girls with mosaicism. Turner syndrome may be diagnosed in infant girls at birth, since they tend to be small and may exhibit severe lymphedema. Evaluation for childhood short stature often leads to the diagnosis. Girls and women with Turner syndrome have an increased risk of aortic coarctation and bicuspid aortic valves; these cardiac abnormalities are more common in patients with a webbed neck. Typical manifestations in adulthood include short stature, hypogonadism, webbed neck, high-arched palate, wide-spaced nipples, hypertension, and

kidney abnormalities (Table 26–15). Emotional disorders are common. Affected women are also more prone to autoimmune disease, particularly thyroiditis, inflammatory bowel disease, and celiac disease.

Hypogonadism presents as “delayed adolescence” (primary amenorrhea, 80%) or early ovarian failure (20%); girls with 45,XO Turner (blood karyotyping) who enter puberty are typically found to have mosaicism if other tissues are karyotyped.

B. Laboratory Findings

Hypogonadism is confirmed in girls who have high serum levels of FSH and LH. A blood karyotype showing 45,XO (or X chromosome abnormalities or mosaicism) establishes the diagnosis. GH and IGF-1 levels are normal.

C. Imaging

A transthoracic ultrasound and MRI scan of the chest and abdomen should be done in all patients with Turner syndrome to determine whether cardiac, aortic, and renal abnormalities are present.

► Treatment

For short stature, GH therapy should be started early, ideally by age 4–6 and before age 12 years. GH is given subcutaneously in doses of 50 mcg/kg/day or 4.5 international units/m²/day; the GH dose is titrated to keep the serum IGF-I levels within 3 SD above the mean for age. Rarely, GH treatment causes pseudotumor cerebri. The oral androgen oxandrolone (0.03–0.05 mg/kg/day) is added after age 10 for girls whose growth is inadequate with GH therapy alone. After age 12 years, estrogen therapy is begun with low doses of transdermal estradiol, with a gradual increase in dose over 2–3 years. Progesterone is added after 2 years of estrogen therapy or if menstrual bleeding occurs. For girls age 12 years or older with Turner mosaicism and spontaneous menses, early oocyte retrieval and cryopreservation should be considered, while weighing the risks of pregnancy.

► Complications & Surveillance

Women with Turner syndrome have a reduced life expectancy due in part to their increased risk of diabetes mellitus (types 1 and 2), hypertension, dyslipidemia, and osteoporosis. Patients are prone to keloid formation after surgery or ear piercing. Annual surveillance should include a blood pressure determination and laboratory evaluations that include a serum TSH, liver enzymes, BUN, creatinine, and fasting serum lipids and glucose. Celiac disease screening (serum TTG IgA Ab) is warranted every 2–5 years for school-age girls and then whenever indicated clinically. Audiology exams are recommended every 1–5 years. Bone mineral densitometries should be measured periodically for women over age 18 years.

Bicuspid aortic valves are common and are associated with an increased risk of infective endocarditis, aortic valvular stenosis or regurgitation, and ascending aortic root dilation and dissection. The risk of aortic dissection is

Table 26–15. Manifestations of Turner syndrome.

Affected Systems	Symptom, Sign, or Condition
Head and neck features	High-arched palate (35%) Low posterior hairline (40%) Micrognathia (60%) Pterygium colli (webbed neck 40%)
Eye abnormalities	Cataracts, corneal opacities Epicantal folds (20%) Strabismus (15%) Ptosis (10%)
Ear abnormalities	Conductive hearing loss (30%) and recurrent otitis media (60%) Low-set and posteriorly rotated ears
Cardiovascular anomalies	Aortic dilation or aneurysm (25% with bicuspid aortic valve) Bicuspid aortic valve (30%) with aortic stenosis or regurgitation Coarctation (14%) and cystic medial necrosis of aorta Hypertension (50%, idiopathic or due to coarctation or kidney disease) Partial anomalous pulmonary venous return (18%)
Gastrointestinal disorders	Achlorhydria Celiac disease (8%) Colon carcinoma Hepatic transaminases, elevated (65%) Inflammatory bowel disease (3%) Telangiectasias with bleeding
Kidney abnormalities (60%)	Horseshoe kidney (10%), duplication or abnormal positioning of renal pelvis or ureters (15%)
Gonadal abnormalities	Gonadal dysgenesis (primary amenorrhea 80%) or early ovarian failure (20%)
Skeletal and extremity abnormalities	Short stature (98%) Broad (shield) chest (30%) with wide-spaced hypoplastic nipples Cubitus valgus of arms (50%) and knock knees (35%) Lymphedema of hands and feet (30%) Madelung wrist deformity (5%) Osteopenia (65%) Scoliosis (10%) Short fourth metacarpals (40%)
CNS disorders	Emotional immaturity (40%) Learning disabilities and ADHD (40%) Sensorineural hearing loss
Skin and nail disorders	Hyperconvex nails Keloid formation Pigmented nevi
Associated conditions	Autoimmune (Hashimoto) thyroiditis (37%) Diabetes mellitus (10%) or glucose intolerance (35%) Dyslipidemia Hyperuricemia Neuroblastoma (1%) Obesity Rheumatoid arthritis

ADHD, attention deficit/hyperactivity disorder; CNS, central nervous system.

increased more than 100-fold in women with Turner syndrome, particularly those with pronounced neck webbing and shield chest. Patients with aortic root enlargement are usually treated with beta-blockade and serial imaging.

About 5% of women with Turner syndrome experience natural pregnancy and even more can become pregnant with oocyte donation. Such pregnancies are very high-risk, with increased fetal morbidity and preeclampsia. During pregnancy, women with Turner syndrome have a 2% risk of

aortic dissection or rupture, so they require close monitoring with repeated echocardiography; those with aortic root diameter 4 cm or more are delivered by elective caesarean section, whereas those with an aortic root diameter less than 4 cm may deliver vaginally.

Partial anomalous pulmonary vein connections can lead to left-to-right shunting of blood. Adults with Turner syndrome also have a high incidence of ECG abnormalities, such as long QT syndrome.

Patients with the classic 45,XO karyotype have a high risk of renal structural abnormalities, whereas those with 46,X/abnormal X are more prone to malformations of the urinary collecting system.

2. Turner Syndrome Variants

A. 46,X (Abnormal X) Karyotype

Patients with small distal short arm deletions of the X chromosome (Xp-) that include the *SHOX* gene often have short stature and skeletal abnormalities but have a low risk of ovarian failure. Transmission of Turner syndrome from mother to daughter can occur. There may be an increased risk of trisomy 21 in the conceptuses of women with Turner syndrome. Patients with deletions of the long arm of the X chromosome (distal to Xq24) often have amenorrhea without short stature or other features of Turner syndrome. Abnormalities or deletions of other genes located on both the long and short arms of the X chromosome can produce gonadal dysgenesis with few other somatic features.

B. 45,XO/46,XX and 45,XO/46,XY Mosaicism

45,XO/46,XX mosaicism results in a modified form of Turner syndrome. Such girls tend to be taller and may have more gonadal function and fewer other manifestations of Turner syndrome.

45,XO/46,XY mosaicism can produce some manifestations of Turner syndrome. Patients may have ambiguous genitalia or male infertility with an otherwise normal phenotype. Germ cell tumors, such as gonadoblastomas and seminomas, develop in about 10% of patients with 45,XO/46,XY mosaicism; most such tumors are benign.

Dabrowski E et al. Turner syndrome systematic review: spontaneous thelarche and menarche stratified by karyotype. *Horm Res Paediatr*. 2019;92:143. [PMID: 31918426]

Kruszka P et al. Turner syndrome in diverse populations. *Am J Med Genet A*. 2020;182:303. [PMID: 31854143]

CLINICAL USE OF CORTICOSTEROIDS

Prolonged treatment with high-dose corticosteroids causes toxic effects that can be life threatening. Besides oral and parenteral administration, transdermal and inhaled corticosteroids have some systemic absorption and can cause similar adverse effects. Patients should be thoroughly informed of the major possible side effects of treatment: insomnia, cognitive and personality changes, weight gain with central obesity, skin thinning and bruising, striae, muscle weakness, polyuria, renal calculi, diabetes mellitus, glaucoma, cataracts, sex hormone suppression, candidiasis, and opportunistic infections (Table 26–16). Prolonged high-dose corticosteroids also increase the risk of hypertension, dyslipidemia, myocardial infarction, stroke, atrial fibrillation or flutter, and heart failure. Gastric ulceration is more common with high-dose corticosteroids, particularly when patients take NSAIDs concurrently. High-dose inhaled corticosteroids predispose to oral thrush and

pulmonary nontuberculous mycobacterial infection. To reduce risks, the dosage and duration of corticosteroid administration must be minimized. Immediately following inhaled corticosteroids, proper mouth-washing and gargling can reduce systemic absorption.

Prolonged oral, inhaled, intravenous, or high-dose topical corticosteroid therapy commonly suppresses pituitary ACTH secretion, causing secondary adrenal insufficiency. Adrenal crisis occurs in 5–10% of such patients yearly with an estimated 6% associated mortality.

Most corticosteroids (dexamethasone, prednisone, hydrocortisone, deflazacort, budesonide) are metabolized by the enzyme CYP3A4. When drugs that inhibit CYP3A4 are administered along with even modest doses of corticosteroids (oral, inhaled, intravenous), the blood levels of the corticosteroids rise and can cause iatrogenic Cushing syndrome and secondary adrenal insufficiency. Medications that strongly inhibit CYP3A4 include itraconazole, ketoconazole, nefazodone, protease inhibitors and cobicistat.

In pregnancy, corticosteroids taken by the mother are transmitted across the placenta to the fetus, causing adverse effects on fetal growth and development as well as childhood cognition and behavior. Therefore, women who are to receive high-dose corticosteroids should be screened for pregnancy and counseled to use contraception.

Osteoporotic fractures (especially vertebral) ultimately occur in about 40% of patients receiving long-term corticosteroid therapy. Osteoporotic fractures can occur even in patients receiving long-term corticosteroid therapy at relatively low doses (eg, 5–7.5 mg prednisone daily). The risk of vertebral fractures increases 14-fold and the risk of hip fractures increases 3-fold. Patients at increased risk for corticosteroid osteoporotic fractures include those who are over age 60 or who have a low BMI, pretreatment osteoporosis, a family history of osteoporosis, or concurrent disease that limits mobility. Avascular necrosis of bone (especially hips) develops in about 15% of patients who receive corticosteroids at high doses (eg, prednisone 15 mg daily or more) for more than 1 month with cumulative prednisone doses of 10 g or more.

Bisphosphonates (eg, alendronate) prevent the development of osteoporosis among patients receiving prolonged courses of corticosteroids (Table 26–16). For patients who are unable to tolerate oral bisphosphonates (due to esophagitis, hiatal hernia, or gastritis), parenteral bisphosphonates can be used. Denosumab inhibits bone resorption but may increase the risk of infection compared to bisphosphonates; therefore, the use of denosumab is not recommended for patients receiving high-dose corticosteroid therapy who are already at an increased risk for infection.

The PTH/PTHrP analogs teriparatide and abaloparatide are anabolic agents that are also effective against corticosteroid-induced osteoporosis. They can be given for a 2-year course and increase bone density more effectively than bisphosphonates. For patients who are currently receiving corticosteroid therapy, however, these analogs increase the risk of hypercalcemia and must be used with great caution; they are most useful for patients with

Table 26–16. Management of patients receiving systemic corticosteroids.

Recommendations for prescribing
<ul style="list-style-type: none"> Do not administer systemic corticosteroids unless absolutely indicated or more conservative measures have failed. Keep dosage and duration of administration to the minimum required for adequate treatment.
Monitoring recommendations
<ul style="list-style-type: none"> Screen for tuberculosis with a purified protein derivative (PPD) test or interferon gamma release assay before commencing long-term corticosteroid therapy. Screen for pregnancy in reproductive age women; recommend contraceptive measures. Screen for diabetes mellitus before treatment and then every 3–4 months. Screen for hypertension before treatment and every 3–4 months. Screen for glaucoma and cataracts before treatment, 3 months after treatment inception, and then at least yearly. Monitor plasma potassium for hypokalemia and treat as indicated. Obtain bone densitometry before treatment and then periodically. Treat osteoporosis. Weigh daily. Use dietary measures to avoid obesity and optimize nutrition. Measure height frequently and obtain bone densitometry by DXA every 1–2 years to document the degree of axial spine demineralization and compression. Watch for fungal or yeast infections of skin, nails, mouth, vagina, and rectum, and treat appropriately. With dosage reduction, watch for signs of adrenal insufficiency or corticosteroid withdrawal syndrome.
Patient information
<ul style="list-style-type: none"> Prepare the patient and family for possible adverse effects on mood, memory, and cognitive function. Teach the patient about the symptoms of hyperglycemia. Inform the patient about other possible side effects, particularly weight gain, osteoporosis, and aseptic necrosis of bone. Counsel to avoid smoking and excessive ethanol consumption.
Prophylactic measures
<ul style="list-style-type: none"> Institute a vigorous physical exercise and isometric regimen tailored to each patient's abilities or disabilities. Administer calcium (1 g elemental calcium) and vitamin D₃, 400–800 units orally daily. <ul style="list-style-type: none"> Check spot morning urine for calcium; alter dosage to keep urine calcium concentration < 30 mg/dL (< 7.5 mmol/L). If the patient is receiving thiazide diuretics, check for hypercalcemia, and administer only 500 mg elemental calcium daily. If the patient has preexistent osteoporosis or has been receiving corticosteroids for ≥ 3 months, consider prophylaxis: <ul style="list-style-type: none"> Bisphosphonate such as alendronate (70 mg every week orally), zoledronic acid (5 mg every year intravenously) for up to 3–5 years; Or Teriparatide, 20 mcg subcutaneously daily for up to 2 years Avoid prolonged bed rest that will accelerate muscle weakness and bone mineral loss. Ambulate early after fractures. Avoid elective surgery, if possible. Vitamin A in a daily dose of 20,000 units orally for 1 week may improve wound healing, but it is not prescribed in pregnancy. Fall prevention strategies: walking assistance (cane, walker, wheelchair, handrails) when required due to weakness or balance problems; avoid activities that could cause falls or other trauma. For ulcer prophylaxis, if administering corticosteroids with nonsteroidal anti-inflammatory drugs, prescribe a proton pump inhibitor (not required for corticosteroids alone). Avoid large doses of antacids containing aluminum hydroxide (many popular brands) because aluminum hydroxide binds phosphate and may cause a hypophosphatemic osteomalacia that can compound corticosteroid osteoporosis. Treat hypogonadism. Treat infections aggressively. Consider unusual pathogens. Treat edema as indicated.

osteoporosis who have stopped high-dose corticosteroid therapy. Following a 2-year course of therapy with these analogs, bone loss and fractures occur quickly after discontinuation, so such therapy is usually followed by bisphosphonate therapy in patients with a history of fracture or osteoporosis by bone densitometry. (See Osteoporosis.) It is wise to follow an organized treatment plan such as the one outlined in Table 26–16.

Buckley L et al. Glucocorticoid-induced osteoporosis. *N Engl J Med.* 2018;379:2547. [PMID: 30586507]

Buttgereit F. Views on glucocorticoid therapy in rheumatology: the age of convergence. *Nat Rev Rheumatol.* 2020;16:239. [PMID: 32076129]

Chotiyarnwong P et al. Pathogenesis of glucocorticoid-induced osteoporosis and options for treatment. *Nat Rev Endocrinol.* 2020;16:437. [PMID: 32286516]

27

Diabetes Mellitus & Hypoglycemia

Umesh Masharani, MB, BS, MRCP (UK)

DIABETES MELLITUS



ESSENTIALS OF DIAGNOSIS

Type 1 diabetes

- ▶ Polyuria, polydipsia, and weight loss with random plasma glucose of ≥ 200 mg/dL (11.1 mmol/L).
- ▶ Plasma glucose of ≥ 126 mg/dL (7.0 mmol/L) after an overnight fast, documented on more than one occasion.
- ▶ Ketonemia, ketonuria, or both.
- ▶ Islet autoantibodies are frequently present.

Type 2 diabetes

- ▶ Many patients are over 40 years of age and are obese.
- ▶ Polyuria and polydipsia. Ketonuria and weight loss are uncommon at time of diagnosis. Candidal vaginitis may be an initial manifestation.
- ▶ Plasma glucose of ≥ 126 mg/dL after an overnight fast on more than one occasion. Two hours after 75 g oral glucose, diagnostic values are ≥ 200 mg/dL (11.1 mmol).
- ▶ $\text{HbA}_{1c} \geq 6.5\%$.
- ▶ Hypertension, dyslipidemia, and atherosclerosis are often associated.

► Classification & Pathogenesis

A. Type 1 Diabetes Mellitus

This form of diabetes is due to autoimmune destruction of pancreatic islet B cell. The rate of pancreatic B cell destruction is quite variable, being rapid in some individuals and slow in others. It occurs at any age but most commonly arises in children and young adults with a peak incidence at age 10–14 years. Type 1 diabetes is usually associated with ketosis in its untreated state. Exogenous insulin is therefore required to reverse the catabolic state, prevent ketosis, reduce the hyperglucagonemia, and reduce blood glucose.

Family members of diabetic probands are at increased lifetime risk for developing type 1 diabetes mellitus. A child whose mother has type 1 diabetes has a 3% risk of developing the disease and a 6% risk if the child's father has it. The risk in siblings is related to the number of HLA haplotypes that the sibling shares with the diabetic proband. If one haplotype is shared, the risk is 6% and if two haplotypes are shared, the risk increases to 12–25%. The highest risk is for monozygotic twins, where the concordance rate is 25–50%.

Some patients with a milder expression of type 1 diabetes mellitus initially retain enough B cell function to avoid ketosis, but as their B cell mass diminishes later in life, dependence on insulin therapy develops. Islet cell antibody surveys among northern Europeans indicate that up to 15% of "type 2" diabetic patients may actually have this mild form of type 1 diabetes (latent autoimmune diabetes of adulthood; LADA). Evidence for environmental factors playing a role in the development of type 1 diabetes include the observation that the disease is more common in Scandinavian countries and becomes progressively less frequent in countries nearer and nearer to the equator. Also, the risk for type 1 diabetes increases when individuals who normally have a low risk emigrate to the Northern Hemisphere. For example, Pakistani children born and raised in Bradford, England, have a higher risk for developing type 1 diabetes compared with children who lived in Pakistan all their lives.

► Epidemiologic Considerations

An estimated 34.2 million people (10.5%) in the United States have diabetes mellitus, of whom approximately 5–10% have type 1 diabetes and most of the rest have type 2 diabetes. A third group designated as "other specific types" by the American Diabetes Association (ADA) (Table 27–1) number in the thousands.

Table 27–1. Other specific types of diabetes mellitus.

Genetic defects of pancreatic B cell function
MODY 1 (HNF-4alpha); rare
MODY 2 (glucokinase); less rare
MODY 3 (HNF-1alpha); accounts for two-thirds of all MODY
MODY 4 (PDX1); very rare
MODY 5 (HNF-1beta); very rare
MODY 6 (neuroD1); very rare
Mitochondrial DNA
Wolfram syndrome
Genetic defects in insulin action
Type A insulin resistance
Leprechaunism
Rabson-Mendenhall syndrome
Lipoatrophic diabetes
Diseases of the exocrine pancreas
Endocrinopathies
Drug- or chemical-induced diabetes
Other genetic syndromes (Down, Klinefelter, Turner, others) sometimes associated with diabetes

HNF, hepatic nuclear factor; MODY, maturity-onset diabetes of the young; PDX1, pancreatic duodenal homeobox 1.

Which environmental factor is responsible for the increased risk is not known. Breastfeeding in the first 6 months of life appears to be protective. There is accumulating evidence that improvements in public health and reduced infections (especially parasitic) lead to immune system dysregulation and development of autoimmune disorders such as asthma and type 1 diabetes.

Check point inhibitor immunotherapies for advanced malignancies, such as nivolumab, pembrolizumab, and ipilimumab, can precipitate autoimmune disorders, including type 1 diabetes. The onset of diabetes can be rapid and the patients frequently have diabetic ketoacidosis at presentation. Autoantibodies against islet antigens are only present in about 50% of patients. Patients receiving these drugs should be carefully monitored for the development of diabetes.

Approximately 5% of subjects have no evidence of pancreatic B cell autoimmunity to explain their insulinopenia and ketoacidosis. This subgroup has been classified as “idiopathic type 1 diabetes” and designated as “type 1B.” Although only a minority of patients with type 1 diabetes fall into this group, most of these individuals are of Asian or African origin. About 4% of the West Africans with ketosis-prone diabetes are homozygous for a mutation in *PAX-4* (*Arg133Trp*)—a transcription factor that is essential for the development of pancreatic islets.

B. Type 2 Diabetes Mellitus

Type 2 diabetes is due to non-immune causes of pancreatic B cell loss with variable degree of tissue insensitivity to insulin, that is, insulin resistance. The residual beta cell function is sufficient to prevent ketoacidosis but is inadequate to prevent the hyperglycemia. This form of diabetes used to occur predominantly in adults, but it is now more frequently encountered in children and adolescents.

Genetic and environmental factors combine to cause both the beta cell loss and the insulin resistance. Most epidemiologic data indicate strong genetic influences, since in monozygotic twins over 40 years of age, concordance develops in over 70% of cases within a year whenever type 2 diabetes develops in one twin. Genome wide association studies have identified 143 risk variants and putative regulator mechanisms for type 2 diabetes. A significant number of the identified loci appear to code for proteins that have a role in beta cell function or development. One of the genetic loci with the largest risk effect is *TCF7L2*. This gene codes for a transcription factor involved in the WNT signaling pathway that is required for normal pancreatic development.

Obesity is the most important environmental factor causing insulin resistance. The degree and prevalence of obesity varies among different racial groups with type 2 diabetes. While obesity is apparent in no more than 30% of Chinese and Japanese patients with type 2, it is found in 60–70% of North Americans, Europeans, or Africans with type 2 and approaches 100% of patients with type 2 among Pima Indians or Pacific Islanders from Nauru or Samoa.

Visceral obesity, due to accumulation of fat in the omental and mesenteric regions, correlates with insulin resistance; subcutaneous abdominal fat seems to have less of an association with insulin insensitivity. There are many patients with type 2 diabetes who, while not overtly obese, have increased visceral fat; they are termed the “metabolically obese.” Exercise may affect the deposition of visceral fat as suggested by CT scans of Japanese wrestlers, whose extreme obesity is predominantly subcutaneous. Their daily vigorous exercise program prevents accumulation of visceral fat, and they have normal serum lipids and euglycemia despite daily intakes of 5000–7000 kcal and development of massive subcutaneous obesity.

C. Other Specific Types of Diabetes Mellitus

1. Maturity-onset diabetes of the young (MODY)—This subgroup of monogenic disorders is characterized by non-insulin requiring diabetes with autosomal dominant inheritance and an age at onset of 25 years or younger. Patients are nonobese, and their hyperglycemia is due to impaired glucose-induced secretion of insulin. Six types of MODY have been described (Table 27–1). Except for MODY 2, in which a glucokinase gene is defective, all other types involve mutations of a nuclear transcription factor that regulates islet gene expression. Patients younger than 30 years with endogenous insulin production (urinary C-peptide/creatinine ratio of 0.2 nmol/mmol or higher) and negative autoantibodies are candidates for genetic screening for MODY. The enzyme glucokinase is a rate-limiting step in glycolysis and determines the rate of adenosine triphosphate (ATP) production from glucose and the insulin secretory response in the beta cell. MODY 2, due to glucokinase mutations, is usually quite mild, associated with only slight fasting hyperglycemia and few if any microvascular diabetic complications. MODY 3, due to mutations in hepatic nuclear factor 1 alpha, is the most common form, accounting for two-thirds of all MODY cases. Initially, patients with MODY 3 are responsive to

sulfonylurea therapy but the clinical course is of progressive beta cell failure and eventual need for insulin therapy. Mutations in both alleles of glucokinase present with more severe neonatal diabetes. Mutation in one allele of the pancreatic duodenal homeobox 1 (PDX1) causes diabetes usually at a later age (~ 35 years) than other forms of MODY; mutations in both alleles of PDX1 cause pancreatic agenesis.

2. Diabetes mellitus associated with a mutation of mitochondrial DNA

—Since sperm do not contain mitochondria, only the mother transmits mitochondrial genes to her offspring. Diabetes due to mutations of mitochondrial DNA occurs in less than 2% of patients with diabetes. The most common cause is the A3243G mutation in the gene coding for the tRNA (Leu, UUR). Diabetes usually develops in these patients in their late 30s, and characteristically, they also have hearing loss (maternally inherited diabetes and deafness [MIDD]).

3. Wolfram syndrome—Wolfram syndrome is an autosomal recessive neurodegenerative disorder first evident in childhood. It consists of diabetes insipidus, diabetes mellitus, optic atrophy, and deafness, hence the acronym DIDMOAD. It is due to mutations in a gene named *WFS1*, which encodes a 100.3 KDa transmembrane protein localized in the endoplasmic reticulum. Cranial diabetes insipidus and sensorineural deafness develop during the second decade in 60–75% of patients. Ureterohydronephrosis, neurogenic bladder, cerebellar ataxia, peripheral neuropathy, and psychiatric illness develop later in many patients.

4. Autosomal recessive syndromes—Homozygous mutations in a number of pancreatic transcription factors, *NEUROG3*, *PTF1A*, *RFX6*, and *GLI-similar 3 (GLIS3)*, cause neonatal or childhood diabetes. Homozygous *PTF1A* mutations result in absent pancreas and cerebellar atrophy; *NEUROG3* mutations cause severe malabsorption and diabetes before puberty. Homozygous mutations in *RFX6* cause the Mitchell-Riley syndrome characterized by absence of all islet cell types apart from pancreatic polypeptide cells, hypoplasia of the pancreas and gallbladder, and intestinal atresia. *GLIS3* gene plays a role in transcription of insulin gene, and homozygous mutations cause neonatal diabetes and congenital hypothyroidism. The gene *EIF2AK3* encodes PKR-like ER kinase (PERK), which controls one of the pathways of the unfolded protein response. Absence of PERK leads to inadequate response to ER stress and accelerated beta cell apoptosis. Patients with mutation in this gene have neonatal diabetes, epiphyseal dysplasia, developmental delay, and liver and kidney dysfunction (Wolcott-Rallison syndrome).

5. Diabetes mellitus secondary to other causes—Endocrine tumors secreting growth hormone, glucocorticoids, catecholamines, glucagon, or somatostatin can cause glucose intolerance (Table 27–2). In the first four of these situations, peripheral responsiveness to insulin is impaired. With excess of glucocorticoids, catecholamines, or glucagon, increased hepatic output of glucose is a contributory factor; in the case of catecholamines, decreased insulin release is an additional factor in producing carbohydrate

Table 27–2. Secondary causes of hyperglycemia.

Hyperglycemia due to tissue insensitivity to insulin
Medications (corticosteroids, sympathomimetic drugs, niacin, alpelisib, sirolimus)
Hormonal tumors (acromegaly, Cushing syndrome, glucagonoma, pheochromocytoma)
Liver disease (cirrhosis, hemochromatosis)
Muscle disorders (myotonic dystrophy)
Adipose tissue disorders (lipodystrophy, truncal obesity)
Hyperglycemia due to reduced insulin secretion
Medications (thiazide diuretics, phenytoin, pentamidine, calcineurin inhibitors, atypical antipsychotics)
Hormonal tumors (somatostatinoma, pheochromocytoma)
Pancreatic disorders (pancreatitis, hemosiderosis, hemochromatosis)

intolerance, and with somatostatin, inhibition of insulin secretion is the major factor. Diabetes mainly occurs in individuals with underlying defects in insulin secretion, and hyperglycemia typically resolves when the hormone excess is resolved.

High-titer anti-insulin receptor antibodies that inhibit insulin binding cause a clinical syndrome characterized by severe insulin resistance, glucose intolerance or diabetes mellitus, and acanthosis nigricans. These patients usually have other autoimmune disorders. There are reports of spontaneous remission or remission with cytotoxic therapy.

Many drugs are associated with carbohydrate intolerance or frank diabetes (Table 27–2). The drugs act by decreasing insulin secretion or by increasing insulin resistance or both. Cyclosporine and tacrolimus impair insulin secretion; sirolimus principally increases insulin resistance. These agents contribute to the development of new-onset diabetes after transplantation. Corticosteroids increase insulin resistance but may also have an effect on beta cell function; in a case control study and a large population cohort study, oral corticosteroids doubled the risk for development of diabetes. Thiazide diuretics and beta-blockers modestly increase the risk for diabetes. Treating the hypokalemia due to thiazides may reverse the hyperglycemia. Atypical antipsychotics, particularly olanzapine and clozapine, are associated with increased risk of glucose intolerance. These drugs cause weight gain and insulin resistance but may also impair beta cell function; an increase in rates of diabetic ketoacidosis (DKA) has been reported. Alpelisib is a phosphatidylinositol-3-kinase (PI3K) inhibitor and is approved for use in combination with fulvestrant for hormone receptor-positive, HER2-negative, *PIK3CA*-mutated breast cancer. PI3K is a component of the insulin signaling pathway, and hyperglycemia is a common side effect of alpelisib treatment.

Chronic pancreatitis or subtotal pancreatectomy reduces the number of functioning B cells and can result in a metabolic derangement very similar to that of genetic type 1 diabetes except that a concomitant reduction in pancreatic A cells may reduce glucagon secretion so that relatively lower doses of insulin replacement are needed.

► Metabolic Syndrome (Insulin Resistance Syndrome)

The term metabolic syndrome has been advocated to identify individuals who were at higher risk for development of diabetes and cardiovascular disease. Criteria included waist circumference, glucose levels, blood pressure, triglycerides, and HDL cholesterol. There is, however, no unifying pathophysiologic basis for the syndrome, and in 2010, a WHO expert committee reported that the syndrome lacked utility as a diagnostic or management tool. They observed that there was only modest association between metabolic syndrome and cardiovascular disease, and the definition was outperformed by traditional cardiovascular risk prediction algorithms such as the Framingham risk score. Similarly, fasting glucose conveys a greater risk of incident diabetes than the metabolic syndrome. There is also no evidence that hyperinsulinemia and insulin resistance play a direct role in these metabolic abnormalities.

► Clinical Trials about Optimum Diabetic Glucose Control

Findings of the Diabetes Control and Complications Trial and of the United Kingdom Prospective Diabetes Study have confirmed the beneficial effects of improved glycemic control in both type 1 and type 2 diabetes.

A. Type 1 Diabetes

The Diabetes Control and Complications Trial (DCCT), a long-term therapeutic study involving 1441 patients with type 1 diabetes mellitus, reported that “near” normalization of blood glucose resulted in a delay in the onset and a major slowing of the progression of established microvascular and neuropathic complications of diabetes.

In half of the patients, a mean hemoglobin A_{1c} of 7.2% (normal: less than 6%) and a mean blood glucose of 155 mg/dL (8.6 mmol/L) were achieved using intensive therapy, while in the conventionally treated group, HbA_{1c} averaged 8.9% with an average blood glucose of 225 mg/dL (12.5 mmol/L). Over the study period, which averaged 7 years, there was an approximately 60% reduction in risk between the two groups in regard to diabetic retinopathy, nephropathy, and neuropathy. The intensively treated group also had a nonsignificant reduction in the risk of macrovascular disease of 41% (95% CI, -10% to 68%). Intensively treated patients had a threefold greater risk of serious hypoglycemia as well as a greater tendency toward weight gain. However, there were no deaths definitely attributable to hypoglycemia in any persons in the DCCT study, and no evidence of posthypoglycemic cognitive damage was detected.

Participants in the DCCT study were subsequently enrolled in a follow-up observational study, the Epidemiology of Diabetes Interventions and Complications (EDIC) study. Even though the between-group differences in mean HbA_{1c} narrowed over 4 years, the group assigned to intensive therapy had a lower risk of retinopathy at 4 years, microalbuminuria at 7–8 years, and impaired GFR (less than 60 mL/min/1.73 m²) at 22 years of continued study

follow-up. Moreover, by the end of the 11-year follow-up period, the intensive therapy group had significantly reduced their risk of any cardiovascular disease events by 42% (95% CI, 9% to 23%; P = 0.02). Thus, it seems that the benefits of good glucose control persist even if control deteriorates at a later date.

The general consensus of the ADA is that intensive insulin therapy associated with comprehensive self-management training should be standard therapy in patients with type 1 diabetes mellitus after the age of puberty. Exceptions include those with advanced chronic kidney disease and older adults since the detrimental risks of hypoglycemia outweigh the benefits of tight glycemic control in these groups.

B. Type 2 Diabetes

The United Kingdom Prospective Diabetes Study (UKPDS), a multicenter study, was designed to establish whether the risk of macrovascular or microvascular complications could be reduced by intensive blood glucose control with oral hypoglycemic agents or insulin and whether any particular therapy was more beneficial than the other in type 2 diabetic patients.

Intensive treatment with either sulfonylureas, metformin, combinations of those two, or insulin achieved mean HbA_{1c} levels of 7%. This level of glycemic control decreased the risk of microvascular complications (retinopathy and nephropathy) in comparison with conventional therapy (mostly diet alone), which achieved mean levels of HbA_{1c} of 7.9%. Weight gain occurred in intensively treated patients except when metformin was used as monotherapy. No adverse cardiovascular outcomes were noted regardless of the therapeutic agent. In the overweight or obese subgroup, metformin therapy was more beneficial than diet alone in reducing the number of patients who suffered myocardial infarctions and strokes. Hypoglycemic reactions occurred in the intensive treatment groups, but only one death from hypoglycemia was documented during 27,000 patient-years of intensive therapy.

Tight control of blood pressure (median value 144/82 mm Hg vs 154/87 mm Hg) substantially reduced the risk of microvascular disease and stroke but not myocardial infarction. In fact, reducing blood pressure by this amount had substantially greater impact on microvascular outcomes than that achieved by lowering HbA_{1c} from 7.9% to 7%. An epidemiologic analysis of the UKPDS data showed that every 10 mm Hg decrease in mean systolic blood pressure was associated with 11% reduction in risk for myocardial infarction. More than half of the patients needed two or more medications for adequate therapy of their hypertension, and there was no demonstrable advantage of angiotensin-converting enzyme (ACE) inhibitor therapy over therapy with beta-blockers with regard to diabetes end points. Use of a calcium channel blocker added to both treatment groups appeared to be safe over the long term in this diabetic population despite some controversy in the literature about its safety in patients with diabetes.

Like the DCCT trialists, the UKPDS researchers performed post-trial monitoring to determine whether there

were long-term benefits of having been in the intensively treated glucose and blood pressure arms of the study. The intensively treated group had significantly reduced risk of myocardial infarction (15%, $P = 0.01$) and death from any cause (13%, $P = 0.007$) during the follow-up period. The subgroup of overweight or obese subjects who were initially randomized to metformin therapy showed sustained reduction in risk of myocardial infarction and death from any cause in the follow-up period. Unlike the sustained benefits seen with glucose control, there were no sustained benefits from having been in the more tightly controlled blood pressure group. Both blood pressure groups were at similar risk for microvascular events and diabetes-related end points during the follow-up period.

Thus, the follow-up of the UKPDS type 2 diabetes cohort showed that, as in type 1 diabetes, the benefits of good glucose control persist even if control deteriorates at a later date. Blood pressure benefits, however, last only as long as the blood pressure is well controlled.

► Diabetes Prevention Trials

A. Prevention of Type 1 Diabetes

At the time of diagnosis of type 1 diabetes, there remains significant B cell pancreatic function. This explains why soon after diagnosis, the diabetes goes into partial clinical remission and little or no insulin is required ("honeymoon"). The clinical remission is short-lived, however, and eventually patients lose all B cell function and have more labile glucose control. Studies have been performed to prolong this partial clinical remission using immunomodulatory agents. The CD3 complex is the major signal-transducing element of the T cell receptor, and the anti-CD3 antibodies are believed to modulate the autoimmune response by selectively inhibiting the pathogenic T cells or by inducing regulatory T cells. Phase 1/2 and 2/3 clinical trials of humanized monoclonal antibodies against CD3, hOKT3gamma (Ala-Ala) (teplizumab), and ChAglyCD3 (otelixizumab) delayed but did not completely arrest the decline in insulin production in patients with newly diagnosed type 1 diabetes. A similar phase 2 clinical trial using teplizumab was undertaken in nondiabetic relatives of patients with type 1 diabetes who had two or more diabetes-related antibodies and glucose intolerance. In the 5 years after randomization, 43% of the patients receiving teplizumab and 72% of the placebo group developed diabetes.

B. Prevention of Type 2 Diabetes

The Diabetes Prevention Program studied whether treatment with either diet and exercise or metformin could prevent the onset of type 2 diabetes in overweight men and women aged 25–85 years who had impaired glucose tolerance. Intervention with a low-fat diet and 150 minutes of moderate exercise (equivalent to a brisk walk) per week reduced the risk of progression to type 2 diabetes by 71%. Participants who took metformin 850 mg twice daily reduced their risk of developing type 2 diabetes by 31%, but this intervention was relatively ineffective in those who were either less obese or in the older age group.

Eighty-eight percent of the persons in the Diabetes Prevention Program elected to continue follow up in the Diabetes Prevention Program Outcome Study. At 15 years of follow up, the cumulative incidence of diabetes was 55% in the lifestyle group and 62% in the control group.

► Clinical Findings

A. Symptoms and Signs

1. Type 1 diabetes—A characteristic symptom complex of hyperosmolality and hyperketonemia from the accumulation of circulating glucose and fatty acids typically presents in patients with type 1 diabetes. When absolute insulin deficiency is of acute onset, there is abrupt increase in urination, thirst, blurred vision, weight loss, paresthesias, and altered level of consciousness. Ketoacidosis exacerbates the dehydration and hyperosmolality by producing anorexia and nausea and vomiting, interfering with oral fluid replacement.

A. INCREASED URINATION AND THIRST—These symptoms are consequences of osmotic diuresis secondary to sustained hyperglycemia. The diuresis results in a loss of glucose as well as free water and electrolytes in the urine.

B. BLURRED VISION—As the lenses are exposed to hyperosmolar fluids, blurred vision often develops.

C. WEIGHT LOSS—Despite normal or increased appetite, weight loss is a common feature of type 1 when it develops subacutely. The weight loss is initially due to depletion of water, glycogen, and triglycerides; thereafter, reduced muscle mass occurs as amino acids are diverted to form glucose and ketone bodies. Loss of subcutaneous fat and muscle wasting are features of more slowly developing insulin deficiency. Lowered plasma volume produces symptoms of postural hypotension, which is a serious prognostic sign. Total body potassium loss and the general catabolism of muscle protein contribute to the weakness.

D. PARESTHESIAS—Paresthesias may be present at the time of diagnosis, particularly when the onset is subacute. They reflect a temporary dysfunction of peripheral sensory nerves, which clears as insulin replacement restores glycemic levels closer to normal, suggesting neurotoxicity from sustained hyperglycemia.

E. THE LEVEL OF CONSCIOUSNESS SHOWN BY THE PATIENT—The patient's level of consciousness can vary depending on the degree of hyperosmolality. When insulin deficiency develops relatively slowly and sufficient water intake is maintained, patients remain relatively alert and physical findings may be minimal. When vomiting occurs in response to worsening ketoacidosis, dehydration progresses and compensatory mechanisms become inadequate to keep serum osmolality below 320–330 mOsm/L. Under these circumstances, stupor or even coma may occur. The fruity breath odor of acetone further suggests the diagnosis of DKA.

2. Type 2 diabetes—While increased urination and thirst may be presenting symptoms in some patients with type 2 diabetes, many other patients have an insidious onset of

hyperglycemia and are asymptomatic initially. This is particularly true in obese patients, whose diabetes may be detected only after glycosuria or hyperglycemia is noted during routine laboratory studies. Occasionally, when the disease has been occult for some time, patients may have evidence of neuropathic or cardiovascular complications at the time of presentation. Hyperglycemic hyperosmolar coma can also be present when the serum osmolality exceeds 320–330 mOsm/L; in these cases, patients are profoundly dehydrated, hypotensive, lethargic, or comatose but without the Kussmaul respirations of ketoacidosis.

A. SKIN MANIFESTATIONS—Chronic skin infections are common. Generalized pruritus and symptoms of vaginitis are frequently the initial complaints of women. Diabetes should be suspected in women with chronic candidal vulvovaginitis. Balanoposthitis (inflammation of the foreskin and glans in uncircumcised males) may occur.

Other skin findings include acanthosis nigricans, which is associated with significant insulin resistance. The skin in the axilla, groin, and back of neck is hyperpigmented and hyperkeratotic (Figure 27-1). Eruptive xanthomas on the flexor surface of the limbs and on the buttocks and lipemia retinalis due to hyperchylomicronemia can occur in patients with uncontrolled type 2 diabetes who also have a familial form of hypertriglyceridemia.

B. BODY HABITUS—Overweight or obese patients frequently have type 2 diabetes. Even those who are not significantly obese often have characteristic localization of fat deposits on the upper segment of the body (particularly the abdomen, chest, neck, and face) and relatively less fat on the appendages, which may be quite muscular. This centripetal fat distribution is characterized by a high waist circumference; a waist circumference larger than 40 inches (102 cm) in men and 35 inches (88 cm) in women is associated with an increased risk of diabetes. Mild hypertension is often present in obese patients with diabetes.

C. OBSTETRICAL COMPLICATIONS—Type 2 diabetes should be considered in women who have delivered babies



▲ **Figure 27-1.** Acanthosis nigricans of the nape of the neck, with typical dark and velvety appearance. (Used, with permission, from Umesh Masharani, MB, BS, MRCP [UK].)

larger than 9 lb (4.1 kg) or have had polyhydramnios, pre-eclampsia, or unexplained fetal losses.

B. Laboratory Findings

1. Urine glucose—A convenient method to detect glucosuria is the paper strip impregnated with glucose oxidase and a chromogen system (Clinistix, Diastix), which is sensitive to as little as 100 mg/dL (5.5 mmol) glucose in urine. A normal renal threshold for glucose as well as reliable bladder emptying is essential for interpretation.

Nondiabetic glucosuria (renal glucosuria) is a benign asymptomatic condition wherein glucose appears in the urine despite a normal amount of glucose in the blood, either basally or during a glucose tolerance test. Its cause may vary from mutations in the *SGLT2* gene coding for sodium-glucose transporter 2 (familial renal glucosuria) to one associated with dysfunction of the proximal renal tubule (Fanconi syndrome, chronic kidney disease), or it may merely be a consequence of the increased load of glucose presented to the tubules by the elevated glomerular filtration rate (GFR) during pregnancy. As many as 50% of pregnant women normally have demonstrable sugar in the urine, especially during the third and fourth months. This sugar is practically always glucose except during the late weeks of pregnancy, when lactose may be present.

2. Urine and blood ketones—Qualitative detection of ketone bodies can be accomplished by nitroprusside tests (Acetest or Ketostix). Although these tests do not detect beta-hydroxybutyric acid, which lacks a ketone group, the semiquantitative estimation of ketonuria thus obtained is nonetheless usually adequate for clinical purposes. Many laboratories measure beta-hydroxybutyric acid, and there are meters available (Precision Xtra; Nova Max Plus) for patient use that measures beta-hydroxybutyric acid levels in capillary glucose samples. Beta-hydroxybutyrate levels greater than 0.6 mmol/L require evaluation. Patients with levels greater than 3.0 mmol/L, equivalent to very large urinary ketones, require hospitalization.

3. Plasma or serum glucose—The glucose concentration is 10–15% higher in plasma or serum than in whole blood because structural components of blood cells are absent. A plasma glucose level of 126 mg/dL (7 mmol/L) or higher on more than one occasion after at least 8 hours of fasting is diagnostic of diabetes mellitus (Table 27-3). Fasting plasma glucose levels of 100–125 mg/dL (5.6–6.9 mmol/L) are associated with increased risk of diabetes (impaired fasting glucose tolerance).

4. Oral glucose tolerance test—If the fasting plasma glucose level is less than 126 mg/dL (7 mmol/L) when diabetes is nonetheless suspected, then a standardized oral glucose tolerance test may be done (Table 27-3). In order to optimize insulin secretion and effectiveness, especially when patients have been on a low-carbohydrate diet, a minimum of 150–200 g of carbohydrate per day should be included in the diet for 3 days preceding the test. The patient should eat nothing after midnight prior to the test day. On the morning of the test, patients are then given 75 g of glucose in 300 mL of water. The glucose load is consumed within

Table 27–3. Criteria for the diagnosis of diabetes.

	Normal Glucose Tolerance ¹	Impaired Glucose Tolerance ¹	Diabetes Mellitus ²
Fasting plasma glucose mg/dL (mmol/L)	< 100 (5.6)	100–125 (5.6–6.9)	≥ 126 (7.0)
2 hours after glucose load mg/dL (mmol/L)	< 140 (7.8)	≥ 140–199 (7.8–11.0)	≥ 200 (11.1)
HbA _{1c} (%)	< 5.7	5.7–6.4	≥ 6.5

¹See text for the oral glucose tolerance test protocol.

²A fasting plasma glucose ≥ 126 mg/dL (7.0 mmol) is diagnostic of diabetes if confirmed by *repeat testing*. A fasting plasma glucose ≥ 126 mg/dL (7.0 mmol) and HbA_{1c} ≥ 6.5% on the *same sample* is also diagnostic of diabetes.

5 minutes. The test is performed in the morning because of diurnal variation in oral glucose tolerance; patients should not smoke or be active during the test.

Blood samples for plasma glucose are obtained at 0 and 120 minutes after ingestion of glucose. Table 27–3 provides diagnostic criteria for diabetes mellitus based on the oral glucose tolerance test. An oral glucose tolerance test is normal if the fasting venous plasma glucose value is less than 100 mg/dL (5.6 mmol/L) and the 2-hour value falls below 140 mg/dL (7.8 mmol/L). A fasting value of 126 mg/dL (7 mmol/L) or higher or a 2-hour value of greater than 200 mg/dL (11.1 mmol/L) is diagnostic of diabetes mellitus. Patients with a 2-hour value of 140–199 mg/dL (7.8–11.1 mmol/L) have impaired glucose tolerance. False-positive results may occur in patients who are malnourished, bedridden, or afflicted with an infection or severe emotional stress.

5. Glycated hemoglobin (hemoglobin A_{1c}) measurements—Hemoglobin becomes glycated by ketoamine reactions between glucose and other sugars and the free amino groups on the alpha and beta chains. Only glycation of the N-terminal valine of the beta chain imparts sufficient negative charge to the hemoglobin molecule to allow separation by charge dependent techniques. These charge-separated hemoglobins are collectively referred to as hemoglobin A₁ (HbA₁). The major form of HbA₁ is hemoglobin A_{1c} (HbA_{1c}) where glucose is the carbohydrate. HbA_{1c} comprises 4–6% of total hemoglobin A.

Since HbA_{1c} circulates within red blood cells whose life span lasts up to 120 days, it generally reflects the state of glycemia over the preceding 8–12 weeks, thereby providing an improved method of assessing diabetic control. The HbA_{1c} value, however, is weighted to more recent glucose levels (previous month) and this explains why significant changes in HbA_{1c} are observed with short-term (1 month) changes in mean plasma glucose levels. Measurements should be made in patients with either type of diabetes mellitus at 3- to 4-month intervals. In patients monitoring their own blood glucose levels, HbA_{1c} values provide a valuable check on the accuracy of monitoring. In patients

who do not monitor their own blood glucose levels, HbA_{1c} values are essential for adjusting therapy. The A_{1c} Derived Average Glucose Study reported that the relationship between average glucose in the previous 3 months and HbA_{1c} was $(28.7 \times \text{HbA}_{1c}) - 46.7$. There is, however, substantial individual variability; for HbA_{1c} values between 6.9% and 7.1%, the glucose levels range from 125 mg/dL to 205 mg/dL (6.9–11.4 mmol/L; 95% CIs). For HbA_{1c} of 6%, the mean glucose levels range from 100 mg/dL to 152 mg/dL (5.5–8.5 mmol/L); and for 8% they range from 147 mg/dL to 217 mg/dL (8.1–12.1 mmol/L). For this reason, caution should be exercised in estimating average glucose levels from measured HbA_{1c}.

The accuracy of HbA_{1c} values can be affected by hemoglobin variants or traits. In patients with high levels of hemoglobin F, immunoassays give falsely low values of HbA_{1c}. The National Glycohemoglobin Standardization Program website (www.ngsp.org) has information on the impact of frequently encountered hemoglobin variants and traits on the results obtained with the commonly used HbA_{1c} assays.

Any condition that shortens erythrocyte survival or decreases mean erythrocyte age (eg, recovery from acute blood loss, hemolytic anemia) will falsely lower HbA_{1c}, irrespective of the assay method used because of the extended time that it takes circulating hemoglobin to be glycosylated. Intravenous iron and erythropoietin therapy for treatment of anemia in chronic kidney disease also falsely lower HbA_{1c} levels. Alternative methods such as fructosamine (see below) should be considered for these patients. Vitamins C and E are reported to falsely lower test results possibly by inhibiting glycation of hemoglobin. Conditions that increase erythrocyte survival such as splenectomy for hereditary spherocytosis will falsely raise HbA_{1c} levels. Iron deficiency anemia is also associated with higher HbA_{1c} levels.

HbA_{1c} is endorsed by the ADA as a diagnostic test for type 1 and type 2 diabetes (Table 27–3). A cutoff value of 6.5% (48 mmol/mol) was chosen because the risk for retinopathy increases substantially above this value. *The advantages of using the HbA_{1c} to diagnose diabetes is that there is no need to fast; it has lower intraindividual variability than the fasting glucose test and the oral glucose tolerance test; and it provides an estimate of glucose control for the preceding 2–3 months.* People with HbA_{1c} levels of 5.7–6.4% (39–46 mmol/mol) should be considered at high risk for developing diabetes (prediabetes). This test is not appropriate to use in populations with high prevalence of hemoglobinopathies or in conditions with increased red cell turnover.

6. Serum fructosamine—Serum fructosamine is formed by nonenzymatic glycosylation of serum proteins (predominantly albumin). Since serum albumin has a much shorter half-life than hemoglobin, serum fructosamine generally reflects the state of glycemic control for only the preceding 1–2 weeks. Reductions in serum albumin (eg, nephrotic state, protein-losing enteropathy, or hepatic disease) will lower the serum fructosamine value. When abnormal hemoglobins or hemolytic states affect the interpretation of glycohemoglobin or when a narrower time

frame is required, such as for ascertaining glycemic control at the time of conception in a diabetic woman who has recently become pregnant, serum fructosamine assays offer some advantage. Normal values vary in relation to the serum albumin concentration and are 200–285 mcmol/L when the serum albumin level is 5 g/dL. HbA_{1c} values and serum fructosamine are highly correlated. Serum fructosamine levels of 300, 367, and 430 mcmol/L approximate to HbA_{1c} values of 7%, 8%, and 9%, respectively. Substantial individual variability exists, though, when estimating the likely HbA_{1c} value from the fructosamine measurement.

7. Self-monitoring of blood glucose—Capillary blood glucose measurements performed by patients themselves, as outpatients, are extremely useful. A large number of blood glucose meters are available. All are accurate, but they vary with regard to speed, convenience, size of blood samples required, reporting capability, and cost. Popular models include those manufactured by LifeScan (One Touch), Bayer Corporation (Contour), Roche Diagnostics (Accu-Chek), and Abbott Laboratories (Precision, Free-Style). These blood glucose meters are relatively inexpensive, ranging from \$20 to \$80 each. Test strips remain a major expense, costing about \$0.25 to \$1.50 apiece. Each glucose meter also comes with a lancet device and disposable 26- to 33-gauge lancets. Most meters can store from 100 to 1000 glucose values in their memories and have capabilities to download the values into a computer or smartphone. Some meters are designed to communicate with a specific insulin pump. Contour Next Link meter, for example, communicates with the MiniMed Medtronic pump. The accuracy of data obtained by home glucose monitoring does require education of the patient in sampling and measuring procedures.

The clinician should be aware of the limitations of the self-monitoring glucose systems. The strips have limited lifespans and improper storage (high temperature; open vial) can affect their function. Patients should also be advised not to use expired strips. Increases or decreases in hematocrit can decrease or increase the measured glucose values. Meters and the test strips are calibrated over the glucose concentrations ranging from 60 mg/dL (3.3 mmol/L) to 160 mg/dL (8.9 mmol/L) and the accuracy is not as good for higher and lower glucose levels. When the glucose is less than 60 mg/dL (3.3 mmol/L), the difference between the meter and the laboratory value may be as much as 20%. Glucose oxidase-based amperometric systems underestimate glucose levels in the presence of high oxygen tension. This may be important in the critically ill who are receiving supplemental oxygen; under these circumstances, a glucose dehydrogenase-based system may be preferable. Glucose-dehydrogenase pyrroloquinoline quinone (GDH-PQQ) systems may report falsely high glucose levels in patients who are receiving parenteral products containing nonglucose sugars such as maltose, galactose, or xylose or their metabolites. Some meters are approved for measuring glucose in blood samples obtained at alternative sites such as the forearm and thigh. There is, however, a 5- to 20-minute lag in the glucose response on the arm with respect to the glucose response on the finger.

Forearm blood glucose measurements could therefore result in a delay in detection of rapidly developing hypoglycemia. Impaired circulation to the fingers (for example, in patients with Raynaud disease) will artificially lower fingerstick glucose measurements (pseudohypoglycemia).

8. Continuous glucose monitoring systems—A glucose oxidase-based system to measure glucose concentrations in the interstitial fluid is used by patients who are increasingly using continuous glucose monitoring systems. These systems, manufactured by Medtronic MiniMed, DexCom systems, and Abbott Diagnostics, involve inserting a subcutaneous sensor (rather like a small wire) that measures glucose concentrations continuously in the interstitial fluid for 7–14 days. The DexCom and MiniMed systems transmit glucose data wirelessly to smartphones or to the screens of insulin pumps. Directional arrows indicate rate and direction of change of glucose levels, and alerts can be set for dangerously low or high glucose values. The wearer also gains insight into how particular foods and activities affect their glucose level. The FreeStyle Libre (Abbott Diagnostics) sensor system requires the patient to hold a reading device or a smartphone close to the sensor patch for about a second to see the real time glucose value. The MiniMed system requires calibration with periodic fingerstick glucose levels, which is not necessary for the Dexcom and Freestyle Libre systems. The factory calibrated systems use a calibration function that automatically corrects for sensor drift over the subsequent 10–14 days. A 6-month randomized controlled study of patients with type 1 diabetes showed that adults (25 years and older) using these continuous glucose monitoring systems had improved glycemic control without an increase in the incidence of hypoglycemia. A randomized controlled study of continuous glucose monitoring during pregnancy showed improved glycemic control in the third trimester, lower birth weight, and reduced risk of macrosomia. Summaries of the continuous glucose monitoring data collected over 2–12 weeks can be very helpful. The percentage of “time in range” (glucose levels 70–180 mg/day [3.9–10 mmol/L]), glucose levels that are low or high, and their variability can be assessed. There is a strong correlation between glucose levels that are 70% “time in range” and an HbA_{1c} of approximately 7%.

Many of these systems are covered by insurance. The initial cost is about \$800 to \$1000, and the sensor, which has to be changed every 7 to 14 days, costs \$35 to \$60; the out-of-pocket expense is about \$4000 annually.

9. Lipoprotein abnormalities in diabetes—Circulating lipoproteins are just as dependent on insulin as is the plasma glucose. In type 1 diabetes, moderately deficient control of hyperglycemia is associated with only a slight elevation of LDL cholesterol and serum triglycerides and little if any change in HDL cholesterol. Once the hyperglycemia is corrected, lipoprotein levels are generally normal. However, in patients with type 2 diabetes, a distinct “diabetic dyslipidemia” is characteristic of the insulin resistance syndrome. Its features are a high serum triglyceride level (300–400 mg/dL [3.4–4.5 mmol/L]), a low

HDL cholesterol (less than 30 mg/dL [0.8 mmol/L]), and a qualitative change in LDL particles, producing a smaller dense particle whose membrane carries supranormal amounts of free cholesterol. These smaller dense LDL particles are more susceptible to oxidation, which renders them more atherogenic. Measures designed to correct the obesity and hyperglycemia, such as exercise, diet, and hypoglycemic therapy, are the treatment of choice for diabetic dyslipidemia, and in occasional patients in whom normal weight was achieved, all features of the lipoprotein abnormalities cleared. Since primary disorders of lipid metabolism may coexist with diabetes, persistence of lipid abnormalities after restoration of normal weight and blood glucose should prompt a diagnostic workup and possible pharmacotherapy of the lipid disorder. Chapter 28 discusses these matters in detail.

American Diabetes Association. 6. Glycemic Targets: *Standards of Medical Care in Diabetes*—2021. *Diabetes Care*. 2021;44:S73. [PMID: 33298417]

Treatment

A. Diet

A well-balanced, nutritious diet remains a fundamental element of therapy. There is no specific recommendation on the percentage of calories that should come from carbohydrate, protein, and fat. The macronutrient proportions should be individualized based on the patient's eating patterns, preferences, and metabolic goals. In general, most patients with diabetes consume about 45% of their total daily calories in the form of carbohydrates, 25–35% in the form of fat, and 10–35% in the form of protein. In patients with type 2 diabetes, limiting the carbohydrate intake and substituting some of the calories with monounsaturated fats, such as olive oil, rapeseed (canola) oil, or the oils in nuts and avocados, can lower triglycerides and increase HDL cholesterol. A Mediterranean-style eating pattern (a diet supplemented with walnuts, almonds, hazelnuts, and olive oil) has been shown to improve glycemic control and lower combined endpoints for cardiovascular events and stroke. In those patients with obesity and type 2 diabetes, weight reduction by caloric restriction is an important goal of the diet (see Chapter 29). Patients with type 1 diabetes or type 2 diabetes who take insulin should be taught "carbohydrate counting," so they can administer their insulin bolus for each meal based on its carbohydrate content.

The current recommendations for saturated fats and dietary cholesterol intake for people with diabetes are the same as for the general population. Saturated fats should be limited to less than 10% of daily calories and dietary cholesterol intake should be less than 300 mg/day. For those patients with kidney disease, dietary protein should be maintained at the recommended daily allowance of 0.8 g/kg/day. Exchange lists for meal planning can be obtained from the American Diabetes Association and its affiliate associations or from the American Dietetic Association (<http://www.eatright.org>), 216 W. Jackson Blvd., Chicago, IL 60606 (312-899-0040).

1. Dietary fiber—Plant components such as cellulose, gum, and pectin are indigestible by humans and are termed dietary "fiber." Insoluble fibers such as cellulose or hemicellulose, as found in bran, tend to increase intestinal transit and may have beneficial effects on colonic function. In contrast, soluble fibers such as gums and pectins, as found in beans, oatmeal, or apple skin, tend to retard nutrient absorption rates so that glucose absorption is slower and hyperglycemia may be slightly diminished. Although its recommendations do not include insoluble fiber supplements such as added bran, the ADA recommends food such as oatmeal, cereals, and beans with relatively high soluble fiber content as staple components of the diet in diabetics. High soluble fiber content in the diet may also have a favorable effect on blood cholesterol levels.

2. Glycemic index—The glycemic index of a carbohydrate containing food is determined by comparing the glucose excursions after consuming 50 g of test food with glucose excursions after consuming 50 g of reference food (white bread):

$$\text{Glycemic index} = \frac{\text{Blood glucose area under the curve (3h) for test food}}{\text{Blood glucose area under the curve (3h) for reference food}} \times 100$$

Eating low glycemic index foods results in lower glucose levels after meals. Low glycemic index foods have values of 55 or less and include many fruits, vegetables, grainy breads, pasta, and legumes. High glycemic index foods have values of 70 or greater and include baked potato, white bread, and white rice. Glycemic index is lowered by the presence of fats and protein when food is consumed in a mixed meal. Even though it may not be possible to accurately predict the glycemic index of a particular food in the context of a meal, it is reasonable to choose foods with low glycemic index.

3. Artificial and other sweeteners—Saccharin (Sweet N Low), sucralose (Splenda), acesulfame potassium (Sweet One), and rebiana (Truvia) are "artificial" sweeteners that can be used in cooking and baking. Aspartame (NutraSweet) lacks heat stability, so it cannot be used in cooking. None of these sweeteners raise blood glucose levels.

Fructose represents a "natural" sugar substance that is a highly effective sweetener, induces only slight increases in plasma glucose levels, and does not require insulin for its metabolism. However, because of potential adverse effects of large amounts of fructose on raising serum cholesterol, triglycerides, and LDL cholesterol, it does not have any advantage as a sweetening agent in the diabetic diet. This does not preclude, however, ingestion of fructose-containing fruits and vegetables or fructose-sweetened foods in moderation.

Sugar alcohols, also known as polyols or polyalcohol, are commonly used as sweeteners and bulking agents. They occur naturally in a variety of fruits and vegetables but are also commercially made from sucrose, glucose, and starch.

Examples are sorbitol, xylitol, mannitol, lactitol, isomalt, maltitol, and hydrogenated starch hydrolysates (HSH). They are not as easily absorbed as sugar, so they do not raise blood glucose levels as much. Therefore, sugar alcohols are often used in food products that are labeled as “sugar free,” such as chewing gum, lozenges, hard candy, and sugar-free ice cream. However, if consumed in large quantities, they will raise blood glucose and can cause bloating and diarrhea.

B. Medications for Treating Hyperglycemia

The medications for treating type 2 diabetes are listed in Table 27–4.

1. Medications that primarily stimulate insulin secretion by binding to the sulfonylurea receptor on the beta cell—

A. SULFONYLUREAS—The primary mechanism of action of the sulfonylureas is to stimulate insulin release from pancreatic B cells.

Sulfonylureas are used in patients with type 2 but not type 1 diabetes, since these medications require functioning pancreatic B cells to produce their effect on blood glucose. Sulfonylureas are metabolized by the liver and apart from acetohexamide, whose metabolite is more active than the parent compound, the metabolites of all the other sulfonylureas are weakly active or inactive. The metabolites are excreted by the kidney and, in the case of the second-generation sulfonylureas, partly excreted in the bile.

Hypoglycemia is a common adverse reaction with the sulfonylureas. Weight gain is also common, especially in the first year of use. The mechanisms of the weight gain include improved glucose control and increased food intake in response to hypoglycemia.

Idiosyncratic reactions are rare, with skin rashes or hematologic toxicity (leukopenia, thrombocytopenia) occurring in less than 0.1% of users.

(1) *First-generation oral sulfonylureas (tolbutamide, tolazamide, acetohexamide, chlorpropamide)*—Tolbutamide is probably best administered in divided doses (eg, 500 mg before each meal and at bedtime); however, some patients require only one or two tablets daily with a maximum dose of 3000 mg/day.

Because of its short duration of action (about 6–10 hours, which is independent of kidney function), tolbutamide is relatively safe to use in kidney disease. Prolonged hypoglycemia has been reported rarely with tolbutamide, mostly in patients receiving antibacterial sulfonamides (sulfisoxazole), phenylbutazone for arthralgias, or the oral azole antifungal medications to treat candidiasis.

Tolazamide, acetohexamide, and chlorpropamide are rarely used. Chlorpropamide has a prolonged biologic effect, and severe hypoglycemia can occur especially in older adults as their renal clearance declines with aging. Its other side effects include alcohol-induced flushing and hyponatremia due to its effect on vasopressin secretion and action.

(2) *Second-generation sulfonylureas (glyburide, glipizide, gliclazide, glimepiride)*—Glyburide, glipizide, gliclazide, and glimepiride are 100–200 times more potent

than tolbutamide. These medications should be used with caution in patients with cardiovascular disease or in elderly patients, in whom prolonged hypoglycemia would be especially dangerous.

The usual starting dose of **glyburide** is 2.5 mg/day, and the average maintenance dose is 5–10 mg/day given as a single morning dose; maintenance doses higher than 20 mg/day are not recommended. Some reports suggest that 10 mg is a maximum daily therapeutic dose, with 15–20 mg having no additional benefit in poor responders and doses over 20 mg actually worsening hyperglycemia. A “Press Tab” formulation of “micronized” glyburide—easy to divide in half with slight pressure if necessary—is available. Glyburide is metabolized in the liver and the metabolic products of glyburide have hypoglycemic activity. This probably explains why assays specific for the unmetabolized compound suggest a plasma half-life of only 1–2 hours, yet the biologic effects of glyburide are clearly persistent 24 hours after a single morning dose in diabetic patients.

Glyburide has few adverse effects other than its potential for causing hypoglycemia, which at times can be prolonged. Flushing has rarely been reported after ethanol ingestion. It does not cause water retention, as chlorpropamide does, but rather slightly enhances free water clearance. Glyburide should not be used in patients with liver failure and chronic kidney disease because of the risk of hypoglycemia. Elderly patients are at particular risk for hypoglycemia even with relatively small daily doses.

The recommended starting dose of **glipizide** is 5 mg/day, with up to 15 mg/day given as a single daily dose before breakfast. When higher daily doses are required, they should be divided and given before meals. The maximum dose recommended by the manufacturer is 40 mg/d, although doses above 10–15 mg probably provide little additional benefit in poor responders and may even be less effective than smaller doses. For maximum effect in reducing postprandial hyperglycemia, glipizide should be ingested 30 minutes before meals, since rapid absorption is delayed when the medication is taken with food.

At least 90% of glipizide is metabolized in the liver to inactive products, and 10% is excreted unchanged in the urine. Glipizide therapy should therefore not be used in patients with liver failure. Because of its lower potency and shorter duration of action, it is preferable to glyburide in elderly patients and for those patients with kidney disease. Glucotrol-XL provides extended release of glipizide during transit through the gastrointestinal tract with greater effectiveness in lowering prebreakfast hyperglycemia than the shorter-duration immediate-release standard glipizide tablets. However, this formulation appears to have sacrificed its lower propensity for severe hypoglycemia compared with longer-acting glyburide without showing any demonstrable therapeutic advantages over glyburide.

Gliclazide (not available in the United States) is another intermediate duration sulfonylurea with a duration of action of about 12 hours. The recommended starting dose is 40–80 mg/day with a maximum dose of 320 mg. Doses of 160 mg and above are given as divided doses before

Table 27–4. Medications for treatment of type 2 diabetes mellitus (oral doses unless otherwise noted).

Drug	Tablet Size	Daily Dose	Duration of Action
Sulfonylureas			
Acetohexamide (Dymelor) (not available in United States)	250 and 500 mg	0.25–1.5 g as single dose or in two divided doses	8–24 hours
Chlorpropamide (Diabinese)	100 and 250 mg	0.1–0.5 g as single dose	24–72 hours
Gliclazide (not available in United States)	80 mg	40–80 mg as single dose; 160–320 mg as divided dose	12 hours
Glimepiride (Amaryl)	1, 2, and 4 mg	Usual dose: 1–4 mg once daily Maximal dose: 8 mg once daily	Up to 24 hours
Glipizide			
(Glucotrol)	5 and 10 mg	Usual dose: 2.5–10 mg twice daily 30 minutes before meals Maximal dose: 20 mg twice daily	6–12 hours
(Glucotrol XL)	2.5, 5, and 10 mg	Usual dose: 2.5–10 mg once daily Maximal dose: 20 mg once daily	Up to 24 hours
Glyburide			
(Dia Beta, Micronase)	1.25, 2.5, and 5 mg	1.25–20 mg as single dose or in two divided doses	Up to 24 hours
(Glynase)	1.5, 3, and 6 mg	1.5–12 mg as single dose or in two divided doses	Up to 24 hours
Tolazamide (Tolinase)	100, 250, and 500 mg	0.1–1 g as single dose or in two divided doses	Up to 24 hours
Tolbutamide (Orinase)	250 and 500 mg	0.5–2 g in two or three divided doses	6–10 hours
Meglitinide Analogs			
Mitiglinide (available in Japan)	5 and 10 mg	5 or 10 mg three times daily before meals	2 hours
Repaglinide (Prandin)	0.5, 1, and 2 mg	Usual dose: 0.5 to 4 mg three times daily 15 minutes before meals Maximal dose: 16 mg daily	3 hours
D-Phenylalanine Derivative			
Nateglinide (Starlix)	60 and 120 mg	60 or 120 mg three times daily before meals	4 hours
Biguanides			
Metformin (Glucophage)	500, 850, and 1000 mg	500–850 mg with meals two or three times daily; 850–1000 mg with breakfast and dinner	4 hours
Metformin, extended release (Glucophage XR) ¹	500, 750, and 1000 mg	500–2000 mg once daily	Up to 24 hours
Thiazolidinediones			
Pioglitazone (Actos)	15, 30, and 45 mg	15–45 mg daily	Up to 24 hours
Rosiglitazone (Avandia)	2, 4, and 8 mg	4–8 mg daily (can be divided)	Up to 24 hours
Alpha-Glucosidase Inhibitors			
Acarbose (Precose)	25, 50, and 100 mg	25–100 mg three times daily just before meals	4 hours
Miglitol (Glyset)	25, 50, and 100 mg	25–100 mg three times daily just before meals	4 hours
Voglibose (not available in United States)	0.2 and 0.3 mg	0.2–0.3 mg three times daily just before meals	4 hours
GLP-1 Receptor Agonists			
Dulaglutide (Trulicity)	0.75-, 1.5-mg single-dose pen or pre-filled syringe	Usual dose: 0.75 mg subcutaneously once weekly Maximal dose: 1.5 mg subcutaneously once weekly	1 week
Exenatide (Byetta)	1.2 mL and 2.4 mL prefilled pens delivering 5 mcg and 10 mcg doses	5 mcg subcutaneously twice daily within 1 hour of breakfast and dinner. Increase to 10 mcg subcutaneously twice daily after about a month. AVOID if eGFR < 30 mL/min/1.73 m ²	6 hours
Exenatide, long-acting release (Byetta LAR, Bydureon)	2 mg (powder)	Suspend in provided diluent and inject subcutaneously.	1 week

(continued)

Table 27–4. Medications for treatment of type 2 diabetes mellitus (oral doses unless otherwise noted). (continued)

Drug	Tablet Size	Daily Dose	Duration of Action
Liraglutide (Victoza)	Prefilled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg	Initial dose: 0.6 mg subcutaneously once daily. Increase to 1.2 mg after a week if no adverse reactions. Maximal dose: 1.8 mg subcutaneously once daily	24 hours
Lixisenatide (Adlyxin, Lyxumia)	3-mL prefilled pens delivering 10- or 20-mcg doses	Initial dose: 10 mcg daily. Increase to 20 mcg daily after 2 weeks.	24 hours
Semaglutide (Ozempic, Rybelsus)	Prefilled pens delivering 0.25 mg or 0.5 mg 1-, 3-, 7-, and 14-mg tablets	Initial dose: 0.25 mg weekly for 1 month and increase to 0.5 mg weekly if no adverse reactions. Maximal dose: 1 mg weekly Initial dose: 3 mg for 1 month and then increase to 7 mg. Take fasting daily with water and wait 30 min to eat. Maximal dose: 14 mg	1 week Daily
DPP-4 Inhibitors			
Alogliptin (Nesina)	6.25, 12.5, and 25 mg	25 mg once daily if eGFR ≥ 60 mL/min/1.73 m ² ; 12.5 mg daily if eGFR 30–59 mL/min/1.73 m ² ; 6.25 mg daily if eGFR < 30 mL/min/1.73 m ²	24 hours
Linagliptin (Tradjenta)	5 mg	5 mg daily	24 hours
Saxagliptin (Onglyza)	2.5 and 5 mg	2.5 mg or 5 mg once daily if eGFR > 50 mL/min/1.73 m ² . 2.5 mg daily if eGFR ≤ 50 mL/min/1.73 m ² or if also taking drugs that are strong CYP3A4/5 inhibitors such as ketoconazole	24 hours
Sitagliptin (Januvia)	25, 50, and 100 mg	100 mg once daily if eGFR > 50 mL/min/1.73 m ² ; 50 mg once daily if eGFR 30–50 mL/min/1.73 m ² ; 25 mg once daily if eGFR < 30 mL/min/1.73 m ²	24 hours
Vildagliptin (Galvus) (not available in United States)	50 mg	50 mg once or twice daily. AVOID if eGFR ≤ 60 mL/min/1.73 m ² or AST/ALT three times upper limit of normal	24 hours
SGLT2 Inhibitors			
Canagliflozin (Invokana)	100 and 300 mg	Usual dose: 100 mg daily. 300 mg can be used if normal eGFR, resulting in lowering the HbA _{1c} an additional ~ 0.1–0.25%. AVOID if eGFR < 45 mL/min/1.73 m ² .	24 hours
Dapagliflozin (Farxiga)	5 and 10 mg	10 mg daily	24 hours
Empagliflozin (Jardiance)	10 and 25 mg	Usual dose: 10 mg daily Maximal dose: 25 mg	24 hours
Ertugliflozin (Steglatro)	5 and 15 mg	Usual dose: 5 mg daily Maximal dose: 15 mg	24 hours
Others			
Bromocriptine (Cycloset)	0.8 mg	0.8 mg daily. Increase weekly by 1 tablet until maximal tolerated dose of 1.6–4.8 mg daily.	24 hours
Colesevelam (Welchol)	625 mg	3 tablets twice daily	24 hours
Pramlintide (Symlin)	5-mL vial containing 0.6 mg/mL; also available as pre-filled pens. Symlin pen 60 or Symlin pen 120	For insulin-treated type 2 patients, start at 60-mcg dose subcutaneously three times daily (10 units on U100 insulin syringe). Increase to 120 mcg three times daily (20 units on U100 insulin syringe) if no nausea for 3–7 days. Give immediately before meal. For type 1 patients, start at 15 mcg three times daily (2.5 units on U100 insulin syringe) and increase by increments of 15 mcg to a maximum of 60 mcg three times daily, as tolerated. To avoid hypoglycemia, lower insulin dose by 50% on initiation of therapy.	2 hours

AST/ALT, aspartate aminotransferase/alanine aminotransferase; eGFR, estimated glomerular filtration rate.

breakfast and dinner. The medication is metabolized by the liver; the metabolites and conjugates have no hypoglycemic effect. An extended-release preparation is available.

Glimepiride has a long duration of effect with a half-life of 5 hours allowing once or twice daily dosing. Glimepiride achieves blood glucose lowering with the lowest dose of any sulfonylurea compound. A single daily dose of 1 mg/day has been shown to be effective, and the maximal recommended dose is 8 mg. It is completely metabolized by the liver to relatively inactive metabolic products.

B. MEGLITINIDE ANALOGS—Repaglinide is structurally similar to glyburide but lacks the sulfonic acid-urea moiety. It acts by binding to the sulfonylurea receptor and closing the adenosine triphosphate (ATP)-sensitive potassium channel. It is rapidly absorbed from the intestine and then undergoes complete metabolism in the liver to inactive biliary products, giving it a plasma half-life of less than 1 hour. The medication therefore causes a brief but rapid pulse of insulin. The starting dose is 0.5 mg three times a day 15 minutes before each meal. The dose can be titrated to a maximum daily dose of 16 mg. Like the sulfonylureas, repaglinide can be used in combination with metformin. Hypoglycemia is the main side effect. Like the sulfonylureas, repaglinide causes weight gain. Metabolism is by cytochrome P450 3A4 isoenzyme, and other medications that induce or inhibit this isoenzyme may increase or inhibit (respectively) the metabolism of repaglinide. The medication may be useful in patients with kidney impairment or in older adults.

Mitiglinide is a benzylsuccinic acid derivative that binds to the sulfonylurea receptor and is similar to repaglinide in its clinical effects. It is approved for use in Japan.

C. D-PHENYLALANINE DERIVATIVE—Nateglinide stimulates insulin secretion by binding to the sulfonylurea receptor and closing the ATP-sensitive potassium channel. It is rapidly absorbed from the intestine, reaching peak plasma levels within 1 hour. It is metabolized in the liver and has a plasma half-life of about 1.5 hours. Like repaglinide, it causes a brief rapid pulse of insulin, and when given before a meal it reduces the postprandial rise in blood glucose. For most patients, the recommended starting and maintenance dose is 120 mg three times a day before meals. Use 60 mg in patients who have mild elevations in HbA_{1c}. Like the other insulin secretagogues, its main side effects are hypoglycemia and weight gain.

2. Medications that primarily lower glucose levels by their actions on the liver, muscle, and adipose tissue—

A. METFORMIN—Metformin is the first-line therapy for patients with type 2 diabetes. It can be used alone or in conjunction with other oral agents or insulin in the treatment of patients with type 2 diabetes. It is ineffective in patients with type 1 diabetes.

Metformin's therapeutic effects primarily derive from the increasing hepatic adenosine monophosphate-activated protein kinase activity, which reduces hepatic gluconeogenesis and lipogenesis. Metformin has a half-life of 1.5–3 hours and is not bound to plasma proteins or metabolized, being excreted unchanged by the kidneys.

The current recommendation is to start metformin at diagnosis. A side benefit of metformin therapy is its tendency to improve both fasting and postprandial hyperglycemia and hypertriglyceridemia in obese patients with diabetes without the weight gain associated with insulin or sulfonylurea therapy. Patients with chronic kidney disease should not be given this medication because failure to excrete it would produce high blood and tissue levels of metformin that could stimulate lactic acid overproduction. In the United States, metformin use is not recommended at or above a serum creatinine level of 1.4 mg/dL in women and 1.5 mg/dL in men. In the United Kingdom, the recommendations are to review metformin use when the serum creatinine exceeds 130 μmol/L (1.5 mg/dL) or the estimated glomerular filtration rate (eGFR) falls below 45 mL/min/1.73 m². The medication should be stopped if the serum creatinine exceeds 150 μmol/L (1.7 mg/dL) or the eGFR is below 30 mL/min/1.73 m². Patients with liver failure or persons with excessive alcohol intake should not receive this medication because of the risk of lactic acidosis.

The maximum dosage of metformin is 2550 mg, although little benefit is seen above a total dose of 2000 mg. It is important to begin with a low dose and increase the dosage very gradually in divided doses—taken with meals—to reduce minor gastrointestinal upsets (anorexia, nausea, vomiting, abdominal discomfort, diarrhea), which occur in up to 20% of patients. A common schedule would be one 500-mg tablet three times a day with meals or one 850- or 1000-mg tablet twice daily at breakfast and dinner. Up to 2000 mg of the extended-release preparation can be given once a day. Lower doses should be used in patients with eGFRs between 30 and 45 mL/min/1.73 m² and in the elderly who are at higher risk for acute kidney injury from reduced renal functional reserve.

The gastrointestinal side effects are dose-related, tend to occur at onset of therapy, and often are transient. However, in 3–5% of patients, therapy may have to be discontinued because of persistent diarrheal discomfort. Patients switching from immediate-release metformin to comparable dose of extended-release metformin may experience fewer gastrointestinal side effects.

Hypoglycemia does not occur with therapeutic doses of metformin, which permits its description as a “euglycemic” or “antihyperglycemic” medication rather than an oral hypoglycemic agent. Dermatologic or hematologic toxicity is rare. Metformin interferes with the calcium dependent absorption of vitamin B₁₂-intrinsic complex in the terminal ileum; vitamin B₁₂ deficiency can occur after many years of metformin use. Periodic screening with vitamin B₁₂ levels should be considered, especially in patients with peripheral neuropathy (which may be erroneously attributed to diabetic neuropathy) or if a macrocytic anemia develops. Increased intake of dietary calcium may prevent the metformin-induced B₁₂ malabsorption.

Lactic acidosis has been reported as a side effect but is uncommon with metformin in contrast to phenformin. Almost all reported cases have involved persons with associated risk factors that should have contraindicated its use (kidney, liver, or cardiopulmonary insufficiency and

alcoholism). Acute kidney injury can occur rarely in certain patients taking metformin who receive radiocontrast agents. Metformin therapy should therefore be temporarily halted on the day of radiocontrast administration and restarted a day or two later after confirmation that kidney function has not deteriorated.

B. THIAZOLIDINEDIONES—Two medications of this class, rosiglitazone and pioglitazone, are available for clinical use. These medications sensitize peripheral tissues to insulin. They bind the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-gamma) and affect the expression of a number of genes. Like the biguanides, this class of medications does not cause hypoglycemia.

Both rosiglitazone and pioglitazone are effective as monotherapy and in combination with sulfonylureas or metformin or insulin, lowering HbA_{1c} by 1–2%. When used in combination with insulin, they can result in a 30–50% reduction in insulin dosage, and some patients can come off insulin completely. The oral dosage of rosiglitazone is 4–8 mg daily and of pioglitazone, 15–45 mg daily; the medications do not have to be taken with food. Rosiglitazone is primarily metabolized by the CYP 2C8 isoenzyme and pioglitazone is metabolized by CYP 2C8 and CYP 3A4.

The combination of a thiazolidinedione and metformin has the advantage of not causing hypoglycemia. Patients inadequately managed on sulfonylureas can do well on a combination of sulfonylurea and rosiglitazone or pioglitazone.

These medications have some additional effects apart from glucose lowering. Rosiglitazone therapy is associated with increases in total cholesterol, LDL cholesterol (15%), and HDL cholesterol (10%). There is a reduction in free fatty acids of about 8–15%. The changes in triglycerides are generally not different from placebo. Pioglitazone in clinical trials lowered triglycerides (9%) and increased HDL cholesterol (15%) but did not cause a consistent change in total cholesterol and LDL cholesterol levels. A prospective randomized comparison of the metabolic effects of pioglitazone and rosiglitazone showed similar effects on HbA_{1c} and weight gain. Small prospective studies have demonstrated that treatment with these medications leads to improvements in the biochemical and histologic features of nonalcoholic fatty liver disease. The thiazolidinediones also may limit vascular smooth muscle proliferation after injury, and there are reports that pioglitazone can reduce neointimal proliferation after coronary stent placement. In one double-blind, placebo-controlled study, rosiglitazone was shown to be associated with a decrease in the ratio of urinary albumin to creatinine excretion.

Safety concerns and some troublesome side effects limit the use of this class of medication. Rosiglitazone use declined when a meta-analysis of 42 randomized clinical trials suggested that this medication increases the risk of angina pectoris or myocardial infarction; the European Medicines Agency suspended the use of rosiglitazone in Europe. In the United States, the FDA established a restricted distribution program. A subsequent large prospective clinical trial (the RECORD study) failed to

confirm the meta-analysis finding and the restrictions were lifted in the United States.

Edema occurs in about 3–4% of patients receiving monotherapy with rosiglitazone or pioglitazone. The edema occurs more frequently (10–15%) in patients receiving concomitant insulin therapy and may result in heart failure. The medications are contraindicated in diabetic individuals with New York Heart Association class III and IV cardiac status. Thiazolidinediones have also been reported as being associated with new onset or worsening macular edema. Apparently, this is a rare side effect, and most of these patients also had peripheral edema. The macular edema resolved or improved once the medication was discontinued.

Troglitazone, the first medication in this class, was withdrawn from clinical use because of medication-associated fatal liver failure. Although rosiglitazone and pioglitazone have not been reported to cause liver injury, the FDA recommends that they should not be used in patients with clinical evidence of active liver disease or pretreatment elevation of the alanine aminotransferase (ALT) level that is 2.5 times greater than the upper limit of normal. Liver biochemical tests should be performed on all patients prior to initiation of treatment and periodically thereafter.

An increase in fracture risk in women (but not men) has been reported with both rosiglitazone and pioglitazone. The fracture risk is in the range of 1.9 per 100 patient-years with the thiazolidinedione as opposed to 1.1 per 100 patient-years on comparison treatment. In at least one study of rosiglitazone, the fracture risk was increased in premenopausal as well as postmenopausal women.

Other side effects include anemia, which occurs in 4% of patients treated with these medications; it may be due to a dilutional effect of increased plasma volume rather than a reduction in red cell mass. Weight gain occurs, especially when the medication is combined with a sulfonylurea or insulin. Some of the weight gain is fluid retention, but there is also an increase in total fat mass. Clinical studies have reported conflicting results regarding an association of bladder cancer with pioglitazone use. A 10-year observational cohort study of patients taking pioglitazone failed to find an association with bladder cancer. A large multipopulation pooled analysis (1.01 million persons over 5.9 million person-years) also failed to find an association between cumulative exposure of pioglitazone or rosiglitazone and incidence of bladder cancer. Another population-based study, however, generating 689,616 person-years of follow-up did find that pioglitazone but not rosiglitazone was associated with an increased risk of bladder cancer.

3. Medications that affect absorption of glucose—Alpha-glucosidase inhibitors competitively inhibit the alpha-glucosidase enzymes in the gut that digest dietary starch and sucrose. Two of these medications—acarbose and miglitol—are available for clinical use in the United States. Voglibose, another alpha-glucosidase inhibitor is available in Japan, Korea, and India. Acarbose and miglitol are potent inhibitors of glucoamylase, alpha-amylase, and sucrase but have less effect on isomaltase and hardly any on trehalase and lactase.

A. ACARBOSE—The recommended starting dose of acarbose is 50 mg orally twice daily, gradually increasing to 100 mg three times daily. For maximal benefit on postprandial hyperglycemia, acarbose should be given with the first mouthful of food ingested. In diabetic patients, it reduces postprandial hyperglycemia by 30–50%, and its overall effect is to lower the HbA_{1c} by 0.5–1%.

The principal adverse effect, seen in 20–30% of patients, is flatulence. This is caused by undigested carbohydrate reaching the lower bowel, where gases are produced by bacterial flora. In 3% of cases, troublesome diarrhea occurs. This gastrointestinal discomfort tends to discourage excessive carbohydrate consumption and promotes improved compliance of type 2 patients with their diet prescriptions. When acarbose is given alone, there is no risk of hypoglycemia. However, if combined with insulin or sulfonylureas, it might increase the risk of hypoglycemia from these agents. A slight rise in hepatic aminotransferases has been noted in clinical trials with acarbose (5% vs 2% in placebo controls, and particularly with doses greater than 300 mg/day). The levels generally return to normal on stopping the medication.

B. MIGLITOL—Miglitol is similar to acarbose in terms of its clinical effects. It is indicated for use in diet- or sulfonylurea-treated patients with type 2 diabetes. Therapy is initiated at the lowest effective dosage of 25 mg orally three times a day. The usual maintenance dose is 50 mg three times a day, although some patients may benefit from increasing the dose to 100 mg three times a day. Gastrointestinal side effects occur as with acarbose. The medication is not metabolized and is excreted unchanged by the kidney. Miglitol should not be used in end-stage chronic kidney disease, when its clearance would be impaired.

4. Incretins—Oral glucose provokes a threefold to fourfold higher insulin response than an equivalent dose of glucose given intravenously. This is because the oral glucose causes a release of gut hormones, principally glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP1), that amplify the glucose-induced insulin release. This “incretin effect” of GLP-1 secretion (but not GIP1 secretion) is reduced in patients with type 2 diabetes; when GLP-1 is infused in patients with type 2 diabetes, it stimulates insulin secretion and lowers glucose levels. GLP-1, unlike the sulfonylureas, has only a modest insulin stimulatory effect at normoglycemic concentrations. This means that GLP-1 has a lower risk for hypoglycemia than the sulfonylureas.

In addition to its insulin stimulatory effect, GLP-1 also has a number of other pancreatic and extrapancreatic effects. It suppresses glucagon secretion and so may ameliorate the hyperglucagonemia that is present in people with diabetes and improve postprandial hyperglycemia. GLP-1 acts on the stomach delaying gastric emptying; the importance of this effect on glucose lowering is illustrated by the observation that antagonizing the deceleration of gastric emptying markedly reduces the glucose lowering effect of GLP-1. GLP-1 receptors are present in the central nervous system and may play a role in the anorectic effect of the drugs. Type 2 diabetic patients undergoing GLP-1

infusion are less hungry; it is unclear whether this is mainly due to a deceleration of gastric emptying or whether there is a central nervous system effect as well.

A. GLP-1 RECEPTOR AGONISTS—GLP-1’s half-life is only 1–2 minutes. It is rapidly proteolyzed by dipeptidyl peptidase 4 (DPP-4) and by other enzymes, such as endopeptidase 24.11, and is also cleared quickly by the kidney. The native peptide, therefore, cannot be used therapeutically. Five GLP-1 receptor agonists with longer half-lives, exenatide, liraglutide, dulaglutide, lixisenatide, and semaglutide, are available for clinical use.

Exenatide (Exendin 4) is a GLP-1 receptor agonist isolated from the saliva of the Gila monster (a venomous lizard) that is more resistant to DPP-4 action and cleared by the kidney. Its half-life is 2.4 hours, and its glucose lowering effect is about 6 hours. Exenatide is dispensed as two fixed-dose pens (5 mcg and 10 mcg). It is injected 60 minutes before breakfast and before dinner. Patients with type 2 diabetes should be prescribed the 5 mcg pen for the first month and, if tolerated, the dose can then be increased to 10 mcg twice a day. The medication is not recommended in patients with eGFR less than 30 mL/min/1.73 m². In clinical trials, adding exenatide therapy to patients with type 2 diabetes already taking metformin or a sulfonylurea, or both, further lowered the HbA_{1c} value by 0.4% to 0.6% over a 30-week period. These patients also experienced a weight loss of 3–6 pounds. Exenatide LAR is a once-weekly preparation that is dispensed as a powder (2 mg). It is suspended in the provided diluent just prior to injection. In comparative clinical trials, the long-acting drug lowers the HbA_{1c} level a little more than the twice daily drug. Low-titer antibodies against exenatide develop in over one-third (38%) of patients, but the clinical effects are not attenuated. High-titer antibodies develop in a subset of patients (~6%), and in about half of these cases, an attenuation of glycemic response has been seen.

Liraglutide is a soluble fatty acid acylated GLP-1 analog. The half-life is approximately 12 hours, allowing the medication to be injected once a day. The dosing is initiated at 0.6 mg daily, increased after 1 week to 1.2 mg daily. Some patients may benefit from increasing the dose to 1.8 mg. In clinical trials lasting 26 and 52 weeks, adding liraglutide to the therapeutic regimen (metformin, sulfonylurea, thiazolidinedione) of patients with type 2 diabetes further lowered the HbA_{1c} value. Depending on the dose and design of the study, the HbA_{1c} decline was in the range of 0.6% to 1.5%. The patients had sustained weight loss of 1–6 pounds. Liraglutide at a dose of 3 mg daily has been approved for weight loss.

In a postmarketing multinational study of 9340 patients with type 2 diabetes with known cardiovascular disease, the addition of liraglutide was associated with a lower primary composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (hazard ratio 0.87, *P* = 0.01). Patients taking liraglutide had lower HbA_{1c} levels, weight loss of 2.3 kg, lower systolic blood pressure, and fewer episodes of severe hypoglycemia.

Dulaglutide consists of two GLP-1 analog molecules covalently linked to an Fc fragment of human IgG₄. The GLP-1 molecule has amino acid substitutions that resist

DPP-4 action. The half-life of dulaglutide is about 5 days. The usual dose is 0.75 mg weekly by subcutaneous injection. The maximum recommended dose is 1.5 mg weekly. Dulaglutide monotherapy and combination therapy lowers HbA_{1c} by about 0.7% to 1.6%. Weight loss ranged from 2 pounds to 7 pounds.

Lixisenatide is a synthetic analog of exendin 4 (deletion of a proline and addition of 6 lysines to the C-terminal region) with a half-life of 3 hours. It is dispensed as two fixed-dose pens (10 mcg and 20 mcg). The 10-mcg dose is injected once daily before breakfast for the first 2 weeks, and if tolerated, the dose is then increased to 20 mcg daily. Its clinical effect is about the same as exenatide with HbA_{1c} lowering in the 0.4–0.6% range. Weight loss ranges from 2 pounds to 6 pounds. Antibodies to lixisenatide occur frequently (70%) and ~2.4% with the highest antibody titers have attenuated glycemic response.

Semaglutide is a synthetic analog of GLP-1 with a drug half-life of about 1 week. It has an alpha-aminoisobutyric acid substitution at position 8 that makes the molecule resistant to DPP4 action and a C-18 fatty di-acid chain attached to lysine at position 26 that binds to albumin, which accounts for the drug's long half-life. Semaglutide is dispensed either subcutaneously or orally. There are two pens for subcutaneous injection: one pen delivers a 0.25-mg or 0.5-mg dose and the other pen delivers a 1-mg dose. The recommended dosing is 0.25 mg weekly for 4 weeks and if tolerated the dose is then increased to 0.5 mg per week. The 1-mg per week dose can provide additional glucose lowering effect. Semaglutide monotherapy and combination therapy lowers HbA_{1c} from 1.5% to 1.8%.

The patient must take oral semaglutide fasting with a glass of water and then wait half an hour before eating, drinking, or taking other medicines. The recommended starting dose is 3 mg daily for the first month, with the dose increased to 7–14 mg daily as tolerated and as needed for glucose control.

Side effects—The most frequent adverse reactions of the GLP-1 receptor agonists are nausea (11–40%), vomiting (4–13%), and diarrhea (9–17%). The reactions are more frequent at the higher doses. In clinical trials about 1–5% of participants withdrew from the studies because of the gastrointestinal symptoms.

The GLP-1 receptor agonists have been associated with increased risk of pancreatitis. The pancreatitis was severe (hemorrhagic or necrotizing) in 6 instances, and 2 of these patients died. In the liraglutide and dulaglutide clinical trials, there were 13 and 5 cases of pancreatitis in the drug-treated groups versus 1 and 1 case in the comparator groups, respectively. This translates to about 1.4–2.2 vs 0.6–0.9 cases of pancreatitis per 1000 patient-years. *Patients taking GLP-1 receptor agonists should be advised to seek immediate medical care if they experience unexplained persistent severe abdominal pain.*

There have been rare reports of acute kidney injury in patients taking exenatide. Some of these patients had pre-existing kidney disease, and others had one or more risk factors for kidney disease. A number of the patients reported nausea, vomiting, and diarrhea, and it is possible that these side effects caused volume depletion and

contributed to the development of the kidney injury. Liraglutide, semaglutide, and dulaglutide are metabolized by proteolysis and are preferred choices in patients with kidney failure.

GLP-1 receptor agonists stimulate C-cell neoplasia and cause medullary thyroid carcinoma in rats. Human C-cells express very few GLP-1 receptors, and the relevance to human therapy is unclear. The medications, however, should not be used in patients with personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia (MEN) syndrome type 2.

B. DPP-4 INHIBITORS—An alternate approach to the use of GLP-1 receptor agonists is to inhibit the enzyme DPP-4 and prolong the action of endogenously released GLP-1 and GIP. Four oral DPP-4 inhibitors, sitagliptin, saxagliptin, linagliptin, and alogliptin, are available in the United States for the treatment of type 2 diabetes. An additional DPP-4 inhibitor, vildagliptin, is available in Europe. Other DPP-4 inhibitors—gemigliptin, anagliptin, teneligliptin, trelagliptin, omarigliptin, evogliptin, and gosogliptin—have been approved outside the United States and European Union (Korea, India, Thailand, Japan, Russia, and several South American countries).

Sitagliptin, when used alone or in combination with other diabetes medications, lowers HbA_{1c} by approximately 0.5%. The usual dose of sitagliptin is 100 mg once daily, but the dose is reduced to 50 mg daily if the calculated creatinine clearance is 30–50 mL/min and to 25 mg for clearances less than 30 mL/min. Saxagliptin, when added to the therapeutic regimen (metformin, sulfonylurea, thiazolidinedione) of patients with type 2 diabetes, further lowered the HbA_{1c} value by about 0.7–0.9%. The dose is 2.5 mg or 5 mg orally once a day. The 2.5-mg dose should be used in patients with eGFR less than 50 mL/min/1.73 m².

Alogliptin lowers HbA_{1c} by about 0.5–0.6% when added to metformin, sulfonylurea, or pioglitazone. The usual dose is 25 mg orally daily. The 12.5-mg dose is used in patients with eGFR of 30–60 mL/min/1.73 m²; and 6.25 mg for clearance less than 30 mL/min/1.73 m². Linagliptin lowers HbA_{1c} by about 0.4–0.6% when added to metformin, sulfonylurea, or pioglitazone. The dose is 5 mg orally daily, and since, it is primarily excreted unmetabolized via the bile, no dose adjustment is needed in patients with kidney disease. Vildagliptin lowers HbA_{1c} by about 0.5–1% when added to the therapeutic regimen of patients with type 2 diabetes. The dose is 50 mg once or twice daily.

Side effects—The main adverse effect of DPP-4 inhibitors appears to be a predisposition to nasopharyngitis or upper respiratory tract infection. Hypersensitivity reactions, including anaphylaxis, angioedema, and exfoliative skin conditions (such as Stevens-Johnson syndrome), have been reported. There have also been reports of pancreatitis, but the frequency of the event is unclear. Cases of liver failure have been reported with the use of alogliptin, but it is uncertain if alogliptin was the cause. The medication, however, should be discontinued in the event of liver failure. Rare cases of hepatic dysfunction, including hepatitis,

have been reported with the use of vildagliptin; and liver biochemical testing is recommended quarterly during the first year of use and periodically thereafter. Saxagliptin may increase the risk of heart failure. In a post-marketing study of 16,492 patients with type 2 diabetes, heart failure occurred in 3.5% in the saxagliptin group and 2.8% in the placebo group (hazard ratio 1.27). Patients with the highest risk of heart failure were those who had a history of heart failure or had elevated levels of N-terminal of the prohormone B-type natriuretic peptide (NT-pBNP) or had kidney impairment. In a large post-marketing study, alogliptin, like saxagliptin, was associated with a slightly increased rate of heart failure. The FDA has issued a warning that the DPP-4 inhibitors can occasionally cause joint pains that resolve after stopping the drug.

5. Sodium-glucose co-transporter 2 inhibitors—Glucose is freely filtered by the kidney glomeruli and is reabsorbed in the proximal tubules by the action of sodium-glucose co-transporters (SGLT). Sodium-glucose co-transporter 2 (SGLT2) accounts for about 90% of glucose reabsorption and its inhibition causes glycosuria in people with diabetes, lowering plasma glucose levels. The oral SGLT2 inhibitors canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin are approved for clinical use in the United States. These agents reduce the threshold for glycosuria from a plasma glucose threshold of about a 180 mg/dL to about 40 mg/dL; and lower HbA_{1c} by 0.5–1% when used alone or in combination with other oral agents or insulin. The efficacy is higher at higher HbA_{1c} levels when more glucose is excreted as a result of SGLT2 inhibition. The loss of calories results in modest weight loss of 2–5 kg.

Canagliflozin is dosed at 100 mg daily but up to 300 mg daily can be used in patients with normal kidney function. The dose of dapagliflozin is 10 mg daily but 5 mg daily is the recommended initial dose in patients with hepatic failure. The usual dosage of empagliflozin is 10 mg daily but a higher dose of 25 mg daily can be used. The recommended starting dose of ertugliflozin is 5 mg, but the dose can be increased to 15 mg daily if additional glucose lowering is needed.

Empagliflozin was evaluated in a multinational study of 7020 patients with type 2 diabetes with known cardiovascular disease; the addition of empagliflozin was associated with a lower primary composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (hazard ratio 0.86, $P = 0.04$). The mechanisms regarding the benefit remain unclear. Weight loss, lower blood pressure, and diuresis may have played a role since there were fewer deaths from heart failure in the treated group whereas the rates of myocardial infarction were unaltered. A similar multinational study was performed with the addition of canagliflozin. This was a study of 10,142 patients with type 2 diabetes with known or at increased risk for cardiovascular disease. The canagliflozin treated group had a lower primary composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (hazard ratio 0.86, $P = 0.02$). In a 2019 heart failure study of 4744 patients with NYHA class II, III, or IV heart failure and ejection fraction of less

40%, dapagliflozin reduced the cumulative incidence of worsening heart failure or cardiovascular death (hazard ratio 0.74, $P < 0.001$). Forty-two percent of the patients had diabetes; the findings in patients with and without diabetes were the same. Both empagliflozin and canagliflozin show benefit in terms of progression of albuminuria and kidney injury, possibly by lowering glomerular hyperfiltration. In a 2019 multinational study of 4401 patients with type 2 diabetes and albuminuric chronic kidney disease (eGFR 30–89 mL/min/1.73 m² with albumin [mg] to creatinine [g] ratio > 300 to 5000) and taking an ACE inhibitor or angiotensin receptor blocker, canagliflozin reduced the risk of end-stage kidney disease, the doubling of serum creatinine, and of renal death. In a 2020 multinational study of 4304 patients with chronic kidney disease, dapagliflozin reduced the risk of end-stage kidney disease or death from renal and cardiovascular causes. A third of the patients in the study did not have diabetes and had benefit.

Side effects—As might be expected, the efficacy of the SGLT2 inhibitors is reduced in chronic kidney disease. They can also increase creatinine and decrease eGFR, especially in patients with kidney impairment. Their use is generally not recommended in patients with eGFR less than 45 mL/min/1.73 m² and are contraindicated in patients with eGFR less than 30 mL/min/1.73 m². The study of dapagliflozin in chronic kidney disease, however, noted that the drug is safe and beneficial in patients with eGFR as low as 25 mL/min/1.73 m². The main side effects are increased incidence of genital mycotic infections and urinary tract infections affecting ~8–9% of patients. Cases of necrotizing fasciitis of the perineum (Fournier gangrene) have been reported. There have also been reports of cases of pyelonephritis and septicemia requiring hospitalization. The glycosuria can cause intravascular volume contraction and hypotension.

One multinational study with canagliflozin showed an increased risk of amputations, especially of the toes (hazard ratio 1.97). This finding has not been observed in other studies using this drug or with the other SGLT2 inhibitors.

Canagliflozin has been reported to cause a decrease in bone mineral density at the lumbar spine and the hip. In a pooled analysis of eight clinical trials (mean duration 68 weeks), a 30% increase in fractures was observed in patients taking canagliflozin. It is likely that the effect on the bones is a class effect and not restricted to canagliflozin. All the SGLT2 inhibitors cause a modest increase in LDL cholesterol levels (3–8%). Also, in clinical trials, patients taking dapagliflozin had higher rates of breast cancer (nine cases vs none in comparator arms) and bladder cancer (10 cases vs 1 in placebo arm). These cancer rates exceeded the expected rates in age-matched reference diabetes population.

Cases of DKA have been reported with off-label use of SGLT2 inhibitors in patients with type 1 diabetes. Type 1 patients are taught to give less insulin if their glucose levels are not elevated. SGLT2 inhibitors lower glucose levels by changing the renal threshold and not by insulin action. Type 1 patients taking an SGLT2 inhibitor, because the glucose levels are not elevated, may either withhold or

reduce their insulin doses to such a degree as to induce ketoacidosis. *SGLT2 inhibitors should not be used in patients with type 1 diabetes and in those patients labeled as having type 2 diabetes but who are very insulin deficient and ketosis-prone.*

6. Others—Pramlintide is a synthetic analog of islet amyloid polypeptide (IAPP or amylin). When given subcutaneously, it delays gastric emptying, suppresses glucagon secretion, and decreases appetite. It is approved for use both in type 1 diabetes and in insulin-treated type 2 diabetes. In 6-month clinical studies with type 1 and insulin-treated type 2 patients, those taking the medication had an approximately 0.4% reduction in HbA_{1c} and about 1.7 kg weight loss compared with placebo. The HbA_{1c} reduction was sustained for 2 years but some of the weight was regained. The medication is given by injection immediately before the meal. Hypoglycemia can occur, and it is recommended that the short-acting or premixed insulin doses be reduced by 50% when the medication is started. Since the medication slows gastric emptying, recovery from hypoglycemia can be a problem because of delay in absorption of fast-acting carbohydrates. Nausea is the other main side effect, affecting 30–50% of persons, but tends to improve with time. In patients with type 1 diabetes, the initial dose of pramlintide is 15 mcg before each meal and titrated up by 15-mcg increments to a maintenance dose of 30 mcg or 60 mcg before each meal. In patients with type 2 diabetes, the starting dose is 60 mcg premeals increased to 120 mcg in 3 to 7 days if no significant nausea occurs.

Bromocriptine, a dopamine 2 receptor agonist, has been shown to modestly lower HbA_{1c} by 0.1–0.5% when compared to baseline and 0.4–0.5% compared to placebo. Common side effects are nausea, vomiting, dizziness, and headache.

Colesevelam, the bile acid sequestrant, when added to metformin or sulfonylurea or insulin, lowered HbA_{1c} 0.3–0.4% when compared to baseline and 0.5–0.6% compared to placebo. HbA_{1c} lowering, however, was not observed in a single monotherapy clinical trial comparing colesevelam to placebo. Colesevelam use is associated with ~20% increase in triglyceride levels. Other adverse effects include constipation and dyspepsia.

With their modest glucose lowering and significant side effects, using bromocriptine or colesevelam to treat diabetes is not recommended.

7. Medication combinations—Several medication combinations are available in different dose sizes, including glyburide and metformin (Glucovance); glipizide and metformin (Metaglip); repaglinide and metformin (Prandi-Met); rosiglitazone and metformin (Avandamet); pioglitazone and metformin (ACTOplusMet); rosiglitazone and glimepiride (Avandaryl); pioglitazone and glimepiride (Duetact); sitagliptin and metformin (Janumet); saxagliptin and metformin XR (Kombiglyze XR); linagliptin and metformin (Jentadueto); alogliptin and metformin (Kazano); alogliptin and pioglitazone (Oseni); dapagliflozin and metformin (Xigduo); canagliflozin and metformin (Invokamet); empagliflozin and metformin (Synjardy); empagliflozin and linagliptin (Glyxambi); empagliflozin, linagliptin, and metformin (Trijardy); ertugliflozin and metformin (Segluoromet); ertugliflozin and sitagliptin (Steglujan); insulin degludec and liraglutide (Xultophy); and insulin glargine and lixisenatide (Soliqua). These medication combinations, however, limit the clinician's ability to optimally adjust dosage of the individual medications and for that reason are not recommended.

C. Insulin

Insulin is indicated for type 1 diabetes as well as for type 2 diabetic patients with insulinopenia whose hyperglycemia does not respond to diet therapy either alone or combined with other hypoglycemic medications.

1. Characteristics of available insulin preparations

Human insulin is dispensed as either regular (R) or NPH (N) formulations. Six analogs of human insulin—three rapidly acting (insulin lispro, insulin aspart, insulin glulisine) and three long-acting (insulin glargine, insulin detemir, and insulin degludec)—are available for clinical use. Insulin preparations differ with respect to the time of onset and duration of their biologic action (Table 27–5). All currently available insulins contain less than 10 ppm of proinsulin and are labeled as “purified.” These purified insulins preserve their potency, so that refrigeration

Table 27–5. Summary of bioavailability characteristics of the insulins.

Insulin Preparations ¹	Onset of Action	Peak Action	Effective Duration
Insulins lispro, aspart, ^{2,3} glulisine	5–15 minutes	1–1.5 hours	3–4 hours
Human regular	30–60 minutes	2 hours	6–8 hours
Human NPH	2–4 hours	6–7 hours	10–20 hours
Insulin glargine	0.5–1 hour	Flat	~24 hours
Insulin detemir	0.5–1 hour	Flat	17 hours
Insulin degludec	0.5–1.5 hours	Flat	More than 42 hours
Technosphere inhaled insulin	5–15 minutes	1 hour	3 hours

¹Insulin administered subcutaneously unless otherwise noted.

²Insulin aspart formulated with niacinamide (FiAsp has an ~10-minute faster onset of action).

³Insulin lispro formulated with treprostinil and citrate (Lyumjev has an 11-minute faster onset of action).

is recommended but not crucial. During travel, reserve supplies of insulin can be readily transported for weeks without losing potency if protected from extremes of heat or cold. All the insulins in the United States are available in a concentration of 100 units/mL (U100) and dispensed in 10-mL vials or 0.3-mL cartridges or prefilled disposable pens. Several insulins are available at higher concentrations: insulin glargine, 300 units/mL (U300); insulin degludec, 200 units/mL (U200); insulin lispro, 200 units/mL (U200); and regular insulin, 500 units/mL (U500).

2. Insulin preparations—See Table 27–6. The rapidly acting insulin analogs and the long-acting insulins are designed for subcutaneous administration, while regular insulin and insulin aspart can also be given intravenously.

A. SHORT-ACTING INSULIN PREPARATIONS

(1) **Regular insulin**—Regular insulin is a short-acting soluble crystalline zinc insulin whose effect appears within 30 minutes after subcutaneous injection and lasts 5–7 hours when usual quantities are administered. Intravenous infusions of regular insulin are particularly useful in the treatment of DKA and during the perioperative management of patients with diabetes who require insulin. For markedly insulin-resistant persons who would otherwise require large volumes of insulin solution, a U500 preparation of human regular insulin is available both in a vial form and a disposable pen. A U500 insulin syringe should be used if the vial form is dispensed. U500 regular insulin is much more expensive than the U100 concentration and is rarely needed.

(2) **Rapidly acting insulin analogs**—Insulin lispro (Humalog, Admelog) is an insulin analog where the proline at position B28 is reversed with the lysine at B29. Insulin aspart (Novolog) is a single substitution of proline by aspartic acid at position B28. In insulin glulisine (Apidra) the asparagine at position B3 is replaced by lysine and the lysine in position B29 by glutamic acid. These three analogs have less of a tendency to form hexamers, in contrast to human insulin. When injected subcutaneously, the analogs quickly dissociate into monomers and are absorbed very rapidly, reaching peak serum values in as soon as 1 hour—in contrast to regular human insulin, whose hexamers require considerably more time to dissociate and become absorbed. The amino acid changes in these analogs do not interfere with their binding to the insulin receptor, with the circulating half-life, or with their immunogenicity, which are all identical with those of human regular insulin. An insulin aspart formulation (FiAsp) that contains niacinamide (vitamin B₃) has a more rapid initial absorption and its onset of action is about 10 minutes faster than the standard insulin aspart formulation. Because of this more rapid onset of action, the 1-hour (but not 2-hour) postprandial glucose excursions are lower compared to the standard formulation. Similarly, an insulin lispro formulation (Lyumjev) containing trepostinil to induce local vasodilation and citrate to increase vascular permeability has 11 minutes faster onset of action and lower 1- and 2-hour postprandial glucose excursions compared to the standard insulin lispro formulation.

Clinical trials have demonstrated that the optimal times of preprandial subcutaneous injection of comparable doses of the rapidly acting insulin analogs and of regular human insulin are 20 minutes and 60 minutes, respectively, before the meal. The quicker onset of action with the rapidly acting insulin analogs allows the patient to inject insulin just before eating rather than wait for 60 minutes as needed for regular insulin. Another desirable feature of rapidly acting insulin analogs is that their duration of action remains at about 4 hours for most commonly used dosages. This contrasts with regular insulin, whose duration of action is significantly prolonged when larger doses are used.

The rapidly acting analogs are commonly used in pumps. In a double-blind crossover study comparing insulin lispro with regular insulin in insulin pumps, persons using insulin lispro had lower HbA_{1c} values and improved postprandial glucose control with the same frequency of hypoglycemia. In the event of pump failure, however, users of the rapidly acting insulin analogs will have more rapid onset of hyperglycemia and ketosis.

While insulin aspart has been approved for intravenous use (eg, in hyperglycemic emergencies), there is no advantage in using insulin aspart over regular insulin by this route. A U200 concentration of insulin lispro is available in a disposable prefilled pen. The only advantage of the U200 over the U100 insulin lispro preparation is that it delivers the same dose in half the volume.

B. LONG-ACTING INSULIN PREPARATIONS

(1) **NPH (neutral protamine Hagedorn or isophane) insulin**—NPH is an intermediate-acting insulin whose onset of action is delayed to 2–4 hours, and its peak

Table 27–6. Insulin preparations available in the United States.¹

Rapidly acting human insulin analogs
Insulin lispro (Humalog, Lyumjev, Lilly; Admelog, Sanofi)
Insulin aspart (Novolog, FiAsp, Novo Nordisk)
Insulin glulisine (Apidra, Sanofi Aventis)
Short-acting regular insulin
Regular insulin (Lilly, Novo Nordisk)
Technosphere inhaled regular insulin (Afrezza)
Intermediate-acting insulins
NPH insulin (Lilly, Novo Nordisk)
Premixed insulins
70% NPH/30% regular (70/30 insulin—Lilly, Novo Nordisk)
70% NPL/25% insulin lispro (Humalog Mix 75/25—Lilly)
50% NPL/50% insulin lispro (Humalog Mix 50/50—Lilly)
70% insulin aspart protamine/30% insulin aspart (Novolog Mix 70/30—Novo Nordisk)
70% insulin degludec/30 insulin aspart (Ryzodeg, Novo Nordisk)
Long-acting human insulin analogs
Insulin glargine (Lantus (U100), Toujeo (U300), Sanofi Aventis; Basaglar (U100), Lilly)
Insulin detemir (Levemir, Novo Nordisk)
Insulin degludec (Tresiba, Novo Nordisk)

¹All insulins available in the United States are recombinant human or human insulin analog origin. All the above insulins are dispensed at U100 concentration. There is an additional U500 preparation of regular insulin; U300 preparation of insulin glargine; U200 preparation of insulin lispro; U200 preparation of insulin degludec. NPH, neutral protamine Hagedorn.

response is generally reached in about 6–7 hours. The onset of action is delayed by combining 2 parts soluble crystalline zinc insulin with 1 part protamine zinc insulin. This produces equivalent amounts of insulin and protamine, so that neither is present in an uncomplexed form (“isophane”). Because its duration of action is often less than 24 hours (with a range of 10–20 hours), most patients require at least two injections daily to maintain a sustained insulin effect. Occasional vials of NPH insulin have tended to show unusual clumping of their contents or “frosting” of the container, with considerable loss of bioactivity. This instability is rare and occurs less frequently if NPH human insulin is refrigerated when not in use and if bottles are discarded after 1 month of use.

(2) **Insulin glargine**—In this insulin, the asparagine at position 21 of the insulin A chain is replaced by glycine and two arginines are added to the carboxyl terminal of the B chain. The arginines raise the isoelectric point of the molecule closer to neutral making it more soluble in an acidic environment. In contrast, human insulin has an isoelectric point of pH 5.4. Insulin glargine is a clear insulin, which, when injected into the neutral pH environment of the subcutaneous tissue, forms microprecipitates that slowly release the insulin into the circulation. This insulin lasts for about 24 hours without any pronounced peaks and is given once a day to provide basal coverage. This insulin cannot be mixed with the other human insulins because of its acidic pH. When this insulin was given as a single injection at bedtime to type 1 patients in clinical trials, fasting hyperglycemia was better controlled with less nocturnal hypoglycemia when compared to NPH insulin.

A more concentrated form of insulin glargine (U300) is available as an insulin pen. In clinical trials in type 1 patients, U300 use did not result in better control or reduce the rates of hypoglycemia. Although limited clinical data suggest that insulin glargine is safe in pregnancy, it is not approved for this use.

(3) **Insulin detemir**—In this insulin analog, the threonine at position B30 has been removed and a 14-C fatty acid chain (tetradecanoic acid) is attached to the lysine at position 29 by acylation. Its prolonged action is due to dihexamerization and binding of hexamers and dimers to albumin at the injection site as well as binding of the monomer via its fatty acid side chain to albumin in the circulation. The affinity of insulin detemir is fourfold to fivefold lower than that of human soluble insulin and therefore the U100 formulation of insulin detemir has an insulin concentration of 2400 nmol/mL compared with 600 nmol/mL for NPH. The duration of action for insulin detemir is about 17 hours at therapeutically relevant doses. It is recommended that the insulin be injected once or twice a day to achieve a stable basal coverage. It has been approved for use during pregnancy.

(4) **Insulin degludec**—In this insulin analog, the threonine at position B30 has been removed, and the lysine at position B29 is conjugated to hexadecanoic acid via a gamma-L-glutamyl spacer. In the vial, in the presence of phenol and zinc, the insulin is in the form of dihexamers but when injected subcutaneously, it self associates into large multihexameric chains consisting of thousands of

dihexamers. The chains slowly dissolve in the subcutaneous tissue and insulin monomers are steadily released into the systemic circulation. The half-life of insulin degludec is 25 hours. Its onset of action is in 30–90 minutes and its duration of action is more than 42 hours. It is recommended that the insulin be injected once or twice a day to achieve a stable basal coverage. Insulin degludec is available in two concentrations, U100 and U200, and dispensed in prefilled disposable pens.

(5) **Insulin icodex**—This is an insulin analog that is suitable for once weekly injection and is in phase 3 clinical trials.

C. MIXED INSULIN PREPARATIONS—Patients with type 2 diabetes can sometimes achieve reasonable glucose control with just prebreakfast and predinner injections of mixtures of short acting and NPH insulins. The regular insulin or rapidly acting insulin analog is withdrawn first, then the NPH insulin and then injected immediately. Stable premixed insulins (70% NPH and 30% regular) are available as a convenience to patients who have difficulty mixing insulin because of visual problems or impairment of manual dexterity (Table 27–6). Premixed preparations of insulin lispro and NPH insulins are unstable; stability is achieved by replacing the NPH insulin with NPL (neutral protamine lispro). This insulin has the same duration of action as NPH insulin. Premixed combinations of NPL and insulin lispro (75% NPL/25% insulin lispro mixture [Humalog Mix 75/25] and 50% NPL/50% insulin lispro mixture [Humalog Mix 50/50]) are available for clinical use. Similarly, a 70% insulin aspart protamine/30% insulin aspart (NovoLog Mix 70/30) is available. The main advantages of these mixtures are that they can be given within 15 minutes of starting a meal and they are superior in controlling the postprandial glucose rise after a carbohydrate-rich meal. These benefits have not translated into improvements in HbA_{1c} levels when compared with the usual 70% NPH/30% regular mixture. The longer-acting insulin analogs, insulin glargine and insulin detemir, cannot be mixed with either regular insulin or the rapidly acting insulin analogs. Insulin degludec, however, can be mixed and is available as 70% insulin degludec/30% insulin aspart and is injected once or twice a day.

3. Methods of insulin administration

A. INSULIN SYRINGES AND NEEDLES—Plastic disposable syringes are available in 1-mL, 0.5-mL, and 0.3-mL sizes. Three lengths of needles are available: 6 mm, 8 mm, and 12.7 mm. Long needles are preferable in obese patients to reduce variability of insulin absorption. The needles are of 28, 30, and 31 gauges. The 31-gauge needles are almost painless. “Disposable” syringes may be reused until blunting of the needle occurs (usually after three to five injections). Sterility adequate to avoid infection with reuse appears to be maintained by recapping syringes between uses. Cleansing the needle with alcohol may not be desirable since it can dissolve the silicone coating and can increase the pain of skin puncturing.

B. SITES OF INJECTION—Any part of the body covered by loose skin can be used, such as the abdomen, thighs, upper

arms, flanks, and upper buttocks. Preparation with alcohol is not required prior to injection as long as the skin is clean. Rotation of sites is recommended to avoid delayed absorption when fibrosis or lipohypertrophy occurs from repeated use of a single site. Regular insulin is absorbed more rapidly when injected in the deltoid or abdomen compared to thighs and buttocks. Exercise can increase absorption when the injection site is adjacent to the exercise muscle. For most patients, the abdomen is the recommended region for injection because it provides adequate area in which to rotate sites. The effect of anatomic regions appears to be much less pronounced with the analog insulins.

C. INSULIN PEN INJECTOR DEVICES—Insulin pens (Novo Nordisk, and Owen Mumford) eliminate the need for carrying insulin vials and syringes. Smart pens (Companion Medical) that are linked to cell phones can be used to remind the user to take their insulin before meals, calculate doses, and keep track of timing of the doses. Cartridges of insulin lispro and insulin aspart are available for the reusable pens. Disposable prefilled pens are also available for regular insulin (U100 and U500), insulin lispro, insulin aspart, insulin glulisine, insulin detemir, insulin glargin, insulin degludec, NPH, 70% NPH/30% regular, 75% NPL/25% insulin lispro, 50% NPL/50% insulin lispro, 70% insulin aspart protamine/30% insulin aspart, and 70% insulin degludec/30% insulin aspart. Pen needles are available in 29, 31, and 32 gauges and 4-, 5-, 6-, 8-, and 12.7-mm lengths (Novofine; BD).

D. INSULIN PUMPS—In the United States, Medtronic MiniMed, Insulet, and Tandem make battery operated continuous subcutaneous insulin infusion (CSII) pumps. These pumps are small (about the size of a pager) and easy to program. They offer many features, including the ability to set a number of different basal rates throughout the 24 hours and to adjust the time over which bolus doses are given. They also are able to detect pressure build-up if the catheter is kinked. The catheter connecting the insulin reservoir to the subcutaneous cannula can be disconnected, allowing the patient to remove the pump temporarily (eg, for bathing). Omnipod (Insulet Corporation) is an insulin infusion system in which the insulin reservoir and infusion set are integrated into one unit (pod), so there is no catheter (electronic patch pump). The pod, placed on the skin, delivers subcutaneous basal and bolus insulin based on wirelessly transmitted instructions from a personal digital assistant. The great advantage of continuous subcutaneous insulin infusion (CSII) is that it allows for establishment of a basal profile tailored to the patient allowing for better overnight and between meals glucose control. The ability to adjust the basal insulin infusion makes it easier for the patient to manage glycemic excursions that occur with exercise. The pumps have software that can assist the patient to calculate boluses based on glucose reading and carbohydrates to be consumed. They keep track of the time elapsed since the last insulin bolus; the patient is reminded of this when he or she attempts to give additional correction bolus before the effect of the previous bolus has worn off (“insulin on board” feature).

This feature reduces the risk of overcorrecting and subsequent hypoglycemia.

CSII therapy is appropriate for patients with type 1 diabetes who are motivated, mechanically inclined, educated about diabetes (diet, insulin action, treatment of hypoglycemia and hyperglycemia), and willing to monitor their blood glucose four to six times a day. Known complications of CSII include ketoacidosis, which can occur when insulin delivery is interrupted, and skin infections. Another disadvantage is its cost and the time needed of the clinician and staff to initiate therapy. Almost all patients use rapid-acting insulin analogs in their pumps.

V-go (Valeritas) is a mechanical patch pump designed specifically for people with type 2 diabetes who use a basal/bolus insulin regimen. The device is preset to deliver one of three fixed and flat basal rates (20, 30, or 40 units) for 24 hours (at which point it must be replaced) and there is a button that delivers two units per press to help cover meals.

E. CLOSED LOOP SYSTEMS—Algorithms have been devised to use glucose data from the continuous glucose monitoring systems to automatically deliver insulin by continuous subcutaneous insulin infusion pump. These closed loop systems (artificial pancreas) have been shown in clinical studies to improve nighttime glucose control, modestly lower HbA_{1c} levels, and reduce the risk of nocturnal hypoglycemia. The MiniMed 670 G and the Tandem Control-IQ, have been approved for clinical use. The MiniMed 670 G closed loop system uses glucose data from a sensor to automatically adjust basal insulin doses every 5 minutes, targeting a sensor glucose level of 120 mg/dL (6.7 mmol/L). Insulin delivery is suspended when the sensor glucose level falls below or is predicted to fall below target level. The glucose target can be adjusted up to 150 mg/dL (8.3 mmol/L) for physical activity. The Tandem Control-IQ targets a sensor glucose level of 112.5 mg/dL (6.25 mmol/L). The patient is still responsible for bolusing insulin for meals and snacks. There are also Do-It-Yourself closed loop systems using free open-source software. One such system, called the “Loop,” uses the Dexcom G6 sensor, the iPhone, and the Omnipod insulin pump. The “Loop” controller is downloaded on to the iPhone, and it uses the Dexcom G6 sensor glucose measurements (also on the iPhone) to automatically adjust basal insulin delivery on the Omnipod pump. Increasing numbers of type 1 patients use these Do-It-Yourself systems, but they are not approved for use by the FDA. Successful use of these systems requires proficiency at using both the insulin pump and continuous glucose monitor. The systems are expensive; the insulin pump, which needs to be replaced every 4 years, costs about \$6000 and the pump supplies are \$1500 per year. The continuous glucose monitoring system costs approximately \$4000 per year.

F. INHALED INSULIN—Technosphere insulin (Afrezza) is a dry-powder formulation of recombinant human regular insulin that can be inhaled. It consists of 2- to 2.5-mcm crystals of the excipient fumaryl diketopiperazine that provide a large surface area for adsorption of proteins like insulin. The technosphere insulin is rapidly absorbed with peak insulin levels reached in 12–15 minutes and declining

to baseline in 3 hours; the median time to maximum effect with inhaled insulin is approximately 1 hour and declines to baseline by about 3 hours. In contrast, the median time to maximum effect with subcutaneous insulin lispro is about 2 hours and declines to baseline by 4 hours. In clinical trials, technosphere insulin combined with basal insulin was as effective in glucose lowering as rapid-acting insulin analogs combined with basal insulin. It is formulated as a single-use, color-coded cartridge delivering 4, 8, or 12 units immediately before the meal. The manufacturer provides a dose conversion table; patients injecting up to 4 units of rapid-acting insulin analog should use the 4-unit cartridge. Those injecting 5 to 8 units should use the 8-unit cartridge. If the dose is 9–12 units of rapid-acting insulin premeal then one 4-unit cartridge and one 8-unit cartridge or one 12-unit cartridge should be used. The inhaler is about the size of a referee's whistle.

The most common adverse reaction of the inhaled insulin is a cough, affecting about 27% of patients. A small decrease in pulmonary function (forced expiratory volume in 1 second [FEV₁]) is seen in the first 3 months of use, which persists over 2 years of follow-up. Inhaled insulin is contraindicated in patients who smoke and in those with chronic lung disease, such as asthma and chronic obstructive pulmonary disease. Spirometry should be performed to identify potential lung disease prior to initiating therapy. During clinical trials, there were two cases of lung cancer in patients who were taking inhaled insulin and none in the comparator-treated patients. All the patients in whom lung cancer developed had a history of prior cigarette smoking. Cases of lung cancer were also reported in cigarette smokers using a previously available inhaled insulin preparation (Exubera). The incidence rate in the Exubera-treated group was 0.13 per 1000 patient-years, whereas it was 0.03 per 1000 patient-years in the comparator-treated group.

D. Transplantation

1. Pancreas transplantation—All patients with end-stage kidney disease and type 1 diabetes who are candidates for a kidney transplant should be considered potential candidates for a pancreas transplant. Eligibility criteria include age younger than 55 and minimal cardiovascular risk. Contraindications include noncorrectable coronary artery disease, extensive peripheral vascular disease, and significant obesity (weight greater than 100 kg). The pancreas transplant may occur at the same time as kidney transplant or after kidney transplant. Patients undergoing simultaneous pancreas and kidney transplantation have an 83% chance of pancreatic graft survival at 1 year and 69% at 5 years. Solitary pancreatic transplantation in the absence of a need for kidney transplantation is considered only in those rare patients who do not respond to all other insulin therapeutic approaches and who have frequent severe hypoglycemia, or who have life-threatening complications related to their lack of metabolic control. Solitary pancreas transplant graft survival is 78% at 1 year and 54% at 5 years.

2. Islet transplantation—Total pancreatectomy is curative for severe pain syndrome associated with chronic pancreatitis. The pancreatectomy, however, results in surgical

diabetes. Harvesting islets from the removed pancreas and autotransplanting them into the liver (via portal vein) can prevent the development of diabetes or result in "mild" diabetes (partial islet function) that is easier to manage. Since the islets are autologous, no immunosuppression is required. The number of islets transplanted is the main predictor of insulin independence.

People with type 1 diabetes can become insulin independent after receiving islets isolated from a donor pancreas (alloislet transplant). The islets are infused into the portal vein using a percutaneous transhepatic approach, and they lodge in the liver releasing insulin in response to physiologic stimuli. Long-term immunosuppression is necessary to prevent allograft rejection and to suppress the autoimmune process that led to the disease in the first place. Insulin independence for more than 5 years has been demonstrated in patients who got anti-CD3 antibody or anti-thymocyte globulin induction immunosuppression and calcineurin inhibitors, mTor inhibitors, and mycophenolate mofetil as maintenance immunosuppression. One major limitation is the need for more than one islet infusion to achieve insulin independence. This is because of significant loss of islets during isolation and the period prior to engraftment. Widespread alloslet transplantation will depend on improving insulin independence rates with one infusion and also demonstrating that the long-term outcomes are as good as those of pancreas transplant alone.

Kristensen SL et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol*. 2019;7:776. [PMID: 31422062]

Leelarathna L et al. Hybrid closed-loop therapy: where are we in 2021? *Diabetes Obes Metab*. 2021;23:655. [PMID: 33269551]

McGuire DK et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. *JAMA Cardiol*. 2021;6:148. [PMID: 33031522]

► Steps in the Management of Diabetes

A. Distinguishing the Types of Diabetes

An attempt should be made to characterize the diabetes as type 1 or type 2 or other specific types such as MODY, based on the clinical features present and on whether or not ketonuria accompanies the glycosuria. Features that suggest end-organ insulin insensitivity to insulin, such as visceral obesity, acanthosis nigricans, or both, must be identified. The family history should document not only the incidence of diabetes in other members of the family but also the age at onset, association with obesity, the need for insulin, and whether there were complications. For the occasional patient, measurement of GAD65, IAA, ICA 512, and zinc transporter 8 antibodies can help distinguish between type 1 and type 2 diabetes (Table 27–7). Many patients with newly diagnosed type 1 diabetes still have significant endogenous insulin production, and C peptide levels do not reliably distinguish between type 1 and type 2 diabetes.

Table 27–7. Diagnostic sensitivity and specificity of autoimmune markers in patients with newly diagnosed type 1 diabetes mellitus.

	Sensitivity	Specificity
Islet cell antibodies (ICA)	44–100%	96%
Glutamic acid decarboxylase (GAD65)	70–90%	99%
Insulin (IAA)	40–70%	99%
Tyrosine phosphatase (IA-2, ICA 512)	50–70%	99%
Zinc transporter 8 (ZnT8)	50–70%	99%

B. Patient Education (Self-Management Training)

Since diabetes is a lifelong disorder, education of the patient and the family is probably the most important obligation of the clinician who provides care. The best persons to manage a disease that is affected so markedly by daily fluctuations in environmental stress, exercise, diet, and infections are the patients themselves and their families. The “teaching curriculum” should include explanations by the clinician or nurse of the nature of diabetes and its potential acute and chronic hazards and how they can be recognized early and prevented or treated. Self-monitoring of blood glucose should be emphasized, especially in insulin-requiring diabetic patients, and instructions must be given on proper testing and recording of data.

Patients taking insulin should have an understanding of the actions of basal and bolus insulins. They should be taught to determine whether the basal dose is appropriate and how to adjust the rapidly acting insulin dose for the carbohydrate content of a meal. Patients and their families and friends should be taught to recognize signs and symptoms of hypoglycemia and how to treat low glucose reactions. Strenuous exercise can precipitate hypoglycemia, and patients must therefore be taught to reduce their insulin dosage in anticipation of strenuous activity or to take supplemental carbohydrate. Injection of insulin into a site farthest away from the muscles most involved in the exercise may help ameliorate exercise-induced hypoglycemia, since insulin injected in the proximity of exercising muscle may be more rapidly mobilized. Exercise training also increases the effectiveness of insulin, and insulin doses should be adjusted accordingly. Infections can cause insulin resistance, and patients should be instructed on how to manage the hyperglycemia with supplemental rapidly acting insulin.

Advice on personal hygiene, including detailed instructions on foot and dental care, should be provided. All infections (especially pyogenic ones) provoke the release of high levels of insulin antagonists, such as catecholamines or glucagon, and thus bring about a marked increase in insulin requirements. Patients who are taking oral agents may decompensate and temporarily require insulin. Patients should be told about community agencies, such as Diabetes Association chapters, that can serve as a continuing source of instruction.

Finally, vigorous efforts should be made to persuade patients with newly diagnosed diabetes who smoke to give up the habit, since large vessel peripheral vascular disease and debilitating retinopathy are less common in nonsmoking diabetic patients.

C. Medications

Treatment must be individualized on the basis of the type of diabetes and specific needs of each patient. However, certain general principles of management can be outlined for hyperglycemic states of different types.

1. Type 1 diabetes—A combination of rapidly acting insulin analogs and long-acting insulin analogs allows for more physiologic insulin replacement. Table 27–8 illustrates a regimen with a rapidly acting insulin analog and long-acting basal insulin that might be appropriate for a 70-kg person with type 1 diabetes eating meals providing standard carbohydrate intake and moderate to low fat content.

Insulin glargine or insulin degludec is usually given once in the evening to provide 24-hour coverage. There are occasional patients in whom insulin glargine does not last for 24 hours, and in such cases, it needs to be given twice a day. Insulin detemir usually has to be given twice a day to get adequate 24-hour basal coverage. Alternatively, small doses of NPH (~3–4 units) can be given with each meal to provide daytime basal coverage with a larger dose at night.

CSII by portable battery-operated “open loop” devices allow the setting of different basal rates throughout the 24 hours and permit bolus dose adjustments by as little as 0.05-unit increments. The 24-hour basal dosage is usually based on age and body weight. An adolescent might need as much as 0.4 unit/kg/day; a young adult (less than 25 years),

Table 27–8. Examples of intensive insulin regimens using rapidly acting insulin analogs (insulin lispro, aspart, or glulisine) and long-acting insulin analogs (insulin detemir, or insulin glargine or degludec) in a 70-kg man with type 1 diabetes.^{1–3}

	Pre-breakfast	Pre-lunch	Pre-dinner	At Bedtime
Rapidly acting insulin analog	5 units	4 units	6 units	
Insulin detemir ³	6–7 units			8–9 units
OR				
Rapidly acting insulin analog	5 units	4 units	6 units	—
Insulin glargine or degludec ³		—		15–16 units

¹ Assumes that patient is consuming approximately 75 g carbohydrate at breakfast, 60 g at lunch, and 90 g at dinner.

² The dose of rapidly acting insulin can be raised by 1 or 2 units if extra carbohydrate (15–30 g) is ingested or if premeal blood glucose is > 170 mg/dL (9.4 mmol/L).

³ Insulin glargine or insulin detemir must be given as a separate injection.

0.35 unit per/kg/day; and an older adult, 0.25 unit/kg/day. For example, a 70-kg, 30-year-old person may require a basal rate of 0.7 unit per hour throughout the 24 hours with the exception of 3 AM to 8 AM, when 0.8 unit per hour might be appropriate (given the “**dawn phenomenon**”—reduced tissue sensitivity to insulin between 5 AM and 8 AM). The meal bolus varies based on the time of day and the person’s age. Adolescents and young adults usually require 1 unit for about 10 g of carbohydrate. Older adults usually require about 1 unit for 15 g of carbohydrate. The correction factor—how much insulin is needed to lower glucose levels by 50 mg/dL—can be calculated from the insulin-to-carbohydrate ratios. For example, if 1 unit is required for 15 g of carbohydrate, then 1 unit will lower glucose levels by 50 mg/dL. If 1.5 units of insulin are required for 15 g of carbohydrate (that is, 1 unit for 10 g carbohydrate), then 1.5 units of insulin will lower glucose levels by 50 mg/dL (that is, 1 unit will lower glucose level by 33 mg/dL). For a 70-kg 30-year-old person, bolus ratios of 1 unit for 12–15 g of carbohydrate plus 1 unit for 50 mg/dL of blood glucose over a target value of 120 mg/dL would be reasonable starting point. Further adjustments to basal and bolus dosages would depend on the results of blood glucose monitoring. One of the more difficult therapeutic problems in managing patients with type 1 diabetes is determining the proper adjustment of insulin dose when the prebreakfast blood glucose level is high. Occasionally, the prebreakfast hyperglycemia is due to the **Somogyi effect**, in which nocturnal hypoglycemia leads to a surge of counterregulatory hormones to produce high blood glucose levels by 7 AM. However, a more common cause for prebreakfast hyperglycemia is the waning of circulating insulin levels by the morning.

The diagnosis of the cause of prebreakfast hyperglycemia can be facilitated by self-monitoring of blood glucose at 3 AM in addition to the usual bedtime and 7 AM measurements or by analyzing data from the continuous glucose monitor. This is required for only a few nights, and when a particular pattern emerges from monitoring blood glucose levels overnight, appropriate therapeutic measures can be taken. The Somogyi effect can be treated by lowering the basal insulin dose at bedtime or by eating a snack at bedtime. When a waning insulin level is the cause, then either increasing the evening basal insulin dose or shifting it from dinnertime to bedtime (or both) can be effective.

The currently available closed loop systems enable patients to achieve close to normal glucose levels in the morning with a low risk of nocturnal hypoglycemia and improve overall glucose control. All patients with type 1 diabetes who are skilled at using insulin pumps should use these systems.

2. Type 2 diabetes—Therapeutic recommendations are based on the relative contributions of beta cell insufficiency and insulin insensitivity in individual patients. The possibility that the individual patient has a specific etiologic cause for their diabetes should always be considered, especially when the patient does not have a family history of type 2 diabetes or does not have any evidence of central obesity or insulin resistance. Such patients should be evaluated for other types of diabetes such as LADA or MODY

(Table 27-1). Patients with LADA should be prescribed insulin when the disease is diagnosed and treated like patients with type 1 diabetes. It is also important to note that many patients with type 2 diabetes mellitus have a progressive loss of beta cell function and will require additional therapeutic interventions with time.

A. WEIGHT REDUCTION—One of the primary modes of therapy in the obese patient with type 2 diabetes is weight reduction. Normalization of glycemia can be achieved by weight loss and improvement in tissue sensitivity to insulin. A combination of caloric restriction, increased exercise, and behavior modification is required if a weight reduction program is to be successful. Understanding the risks associated with the diagnosis of diabetes may motivate the patient to lose weight.

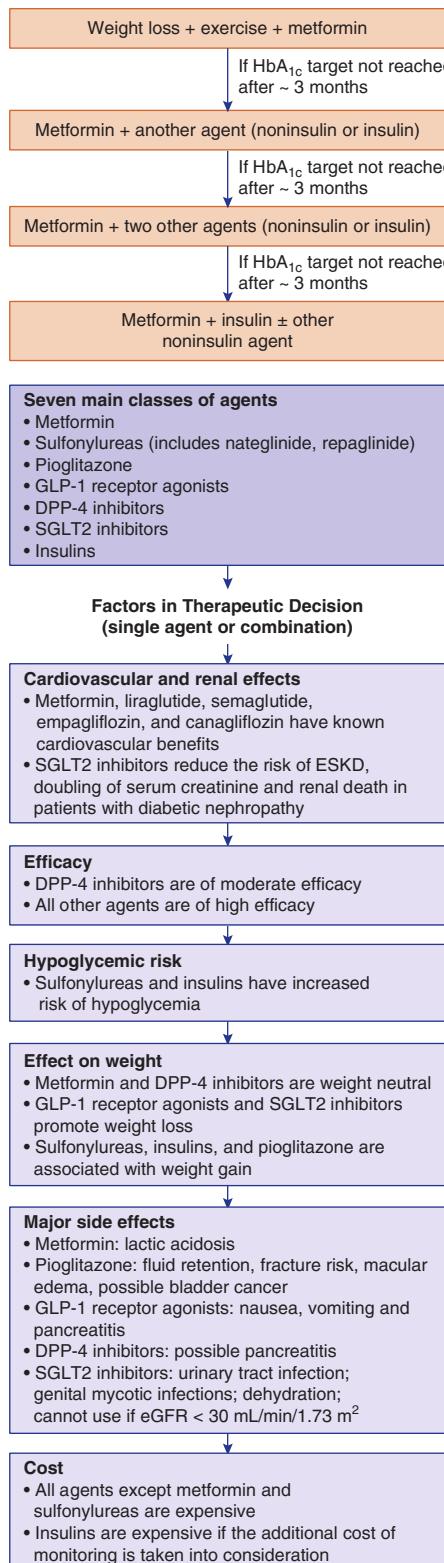
For selected patients, medical or surgical options for weight loss should be considered. Orlistat, phentermine/topiramate, lorcaserin, naltrexone/extended-release bupropion, and high-dose liraglutide (3 mg daily) are weight loss medications approved for use in combination with diet and exercise (see Chapter 29).

Bariatric surgery (Roux-en-Y, gastric banding, gastric sleeve, biliopancreatic diversion/duodenal switch) typically results in substantial weight loss and improvement in glucose levels. A meta-analysis examining the impact of bariatric surgery on patients with diabetes and BMI of 40 kg/m² or greater noted that 82% of patients had resolution of clinical and laboratory manifestations of diabetes in the first 2 years after surgery and 62% remained free of diabetes more than 2 years after surgery. The improvement was most marked in the procedure that caused the greatest weight loss (biliopancreatic diversion/duodenal switch). There was, however, a high attrition of patients available for follow-up, and there was little information about different ethnic types. Weight regain does occur after bariatric surgery, and it can be expected that 20–25% of the lost weight will be regained over 10 years. The impact of this weight gain on diabetes recurrence depends principally on the degree of beta cell dysfunction.

Nonobese patients with type 2 diabetes frequently have increased visceral adiposity—the so-called metabolically obese normal weight patient. There is less emphasis on weight loss, but exercise remains an important aspect of treatment.

B. GLUCOSE-LOWERING AGENTS—Figure 27-2 outlines the treatment approach based on the consensus algorithm proposed by the American Diabetes Association and the European Association for the Study of Diabetes. The current recommendation is to start metformin therapy at diagnosis and not wait to see whether the patient can achieve target glycemic control with weight management and exercise. See discussion of the individual medications, above.

When diabetes is not well controlled with initial therapy (usually metformin), then a second agent should be added. Presence of cardiovascular or kidney disease, or both, will determine the choice of the second agent. Liraglutide, semaglutide, empagliflozin, canagliflozin, and dapagliflozin have improved cardiovascular outcomes.



The SGLT2 inhibitors are especially beneficial in patients with heart failure or diabetic nephropathy, or both. The need for weight loss should lead to the use of GLP-1-receptor agonists in the obese patient with or without coronary artery disease. SGLT2 inhibitors also promote modest weight loss and should be prescribed in the patient with heart failure or diabetic nephropathy. Sulfonylureas have been available for many years and their use in combination with metformin is well established. They do, however, have the propensity of causing hypoglycemia and weight gain. In patients who experience hyperglycemia after a carbohydrate-rich meal (such as dinner), a short-acting secretagogue (repaglinide or nateglinide) before meals may suffice to get the glucose levels into the target range. Patients with severe insulin resistance may be candidates for pioglitazone. Pioglitazone may also reduce the risk for recurrent stroke in patients who have a history of stroke or transient ischemic attack. If two agents are inadequate, then a third agent is added, although data regarding efficacy of such combined therapy are limited.

When the combination of oral agents (and injectable GLP-1 receptor agonists) fails to achieve euglycemia in patients with type 2 diabetes, then insulin treatment should be instituted. Various insulin regimens may be effective. One proposed regimen is to continue the oral combination therapy and then simply add a bedtime dose of NPH or long-acting insulin analog (insulin glargine, detemir, or degludec) to reduce excessive nocturnal hepatic glucose output and improve fasting glucose levels. If the patient does not achieve target glucose levels during the day, then daytime insulin treatment can be initiated. A convenient insulin regimen under these circumstances is a split dose of 70/30 NPH/regular mixture (or Humalog Mix 75/25 or NovoLogMix 70/30) before breakfast and before dinner. If this regimen fails to achieve satisfactory glycemic goals or is associated with unacceptable frequency of hypoglycemic episodes, then a more intensive regimen of multiple insulin injections can be instituted as in patients with type 1 diabetes. Metformin principally reduces hepatic glucose output, and it is reasonable to continue with this medication when insulin therapy is instituted. Pioglitazone, which improves peripheral insulin sensitivity, can be used together with insulin but this combination is associated with more weight gain and peripheral edema. The sulfonylureas, the GLP-1 receptor agonists, the DPP-4 inhibitors, and the SGLT2 inhibitors also have been shown to be of continued benefit. Weight-reducing interventions should continue even after initiation of insulin therapy and may allow for simplification of the therapeutic regimen in the future.

D. Acceptable Levels of Glycemic Control

A reasonable aim of therapy is to approach normal glycemic excursions without provoking severe or frequent hypoglycemia. Table 27–9 summarizes blood glucose and HbA_{1c} goals for different patient groups. The UKPDS study demonstrated that blood pressure control was as significant or more significant than glycemic control in patients with type 2 diabetes regarding the prevention of microvascular as well as macrovascular complications.

▲ **Figure 27–2.** Algorithm for the treatment of type 2 diabetes based on the 2018 recommendations of the consensus panel of the American Diabetes Association/European Association for the Study of Diabetes.

Table 27–9. Glycemic targets for different groups of adults with diabetes.

	Blood Glucose Targets (mg/dL [mmol/L])	HbA _{1c} Target (% [mmol/mol])
Nonpregnant healthy adults	Premeal glucose 90–130 (5–7.2) 1-hour peak < 180 (10) 2-hour peak < 150 (8.3)	< 7 (53). Aim for < 6.5 (48) if it can be achieved without significant hypoglycemia or polypharmacy
Pregnancy	Premeal glucose ≤ 95 (5.3) 1-hour peak ≤ 140 (7.8) 2-hour peak ≤ 120 (6.7)	6–6.5 (42–48). Aim for < 6 (42) if possible without significant hypoglycemia
Older adults Healthy Frail with limited life expectancy	Premeal 90–130 (5–7.2) Bedtime 90–150 (5–8.3) Premeal 100–180 (5.6–10) Bedtime 110–200 (6.1–11.1)	< 7.5 (58) < 8.5 (69)
History of severe hypoglycemia	Premeal 90–150 (5–8.3) Bedtime 100–180 (5.6–10)	< 8 (64)
Hospitalized patient	140–180 (7.8–10)	—
Chronic kidney disease (CKD)	Glycemic targets in CKD are the same as those without CKD. HbA _{1c} and fructosamine values may not be accurate in end-stage kidney disease, and greater reliance should be placed on the home glucose measurements	

E. Complications of Insulin Therapy

1. Hypoglycemia—Hypoglycemic reactions are the most common complications that occur in patients with diabetes who are treated with insulin. The signs and symptoms of hypoglycemia may be divided into those resulting from stimulation of the autonomic nervous system and those from neuroglycopenia (insufficient glucose for normal central nervous system function). When the blood glucose falls to around 54 mg/dL (3 mmol/L), the patient starts to experience both sympathetic (tachycardia, palpitations, sweating, tremulousness) and parasympathetic (nausea, hunger) nervous system symptoms. If these autonomic symptoms are ignored and the glucose levels fall further (to around 50 mg/dL [2.8 mmol/L]), then neuroglycopenic symptoms appear, including irritability, confusion, blurred vision, tiredness, headache, and difficulty speaking. A further decline in glucose can lead to loss of consciousness or even a seizure. With repeated episodes of hypoglycemia, there is adaptation, and autonomic symptoms do not occur until the blood glucose levels are much lower and so the first symptoms are often due to neuroglycopenia. This condition is referred to as “hypoglycemic unawareness.” It has been shown that hypoglycemic unawareness can be reversed by keeping glucose levels high for a period of several weeks. Except for sweating, most of the sympathetic symptoms of hypoglycemia are blunted in patients receiving beta-blocking agents. Though not absolutely contraindicated, these medications must be used with caution in patients with diabetes who require insulin, and beta-1-selective blocking agents are preferred.

Hypoglycemia can occur in a patient taking sulfonylureas, repaglinide, and nateglinide, particularly if the patient is elderly, has kidney or liver disease, or is taking certain other medications that alter metabolism of the sulfonylureas (eg, phenylbutazone, sulfonamides, or warfarin). It occurs more frequently with the use of long-acting

sulfonylureas than with shorter-acting agents. Otherwise, hypoglycemia in insulin-treated patients occurs as a consequence of three factors: behavioral issues, impaired counterregulatory systems, and complications of diabetes.

Behavioral issues include injecting too much insulin for the amount of carbohydrates ingested. Drinking alcohol in excess, especially on an empty stomach, can also cause hypoglycemia. In patients with type 1 diabetes, hypoglycemia can occur during or even several hours after exercise, and so glucose levels need to be monitored and food and insulin adjusted. Some patients do not like their glucose levels to be high, and they treat every high glucose level aggressively. These individuals who “stack” their insulin—that is, give another dose of insulin before the first injection has had its full action—can develop hypoglycemia.

Counterregulatory issues resulting in hypoglycemia include impaired glucagon response, sympatho-adrenal responses, and cortisol deficiency. Patients with diabetes of greater than 5 years in duration lose their glucagon response to hypoglycemia. As a result, they are at a significant disadvantage in protecting themselves against falling glucose levels. Once the glucagon response is lost, their sympatho-adrenal responses take on added importance. Unfortunately, aging, autonomic neuropathy, or hypoglycemic unawareness due to repeated low glucose levels further blunts the sympatho-adrenal responses. Occasionally, Addison disease develops in persons with type 1 diabetes mellitus; when this happens, insulin requirements fall significantly, and unless insulin dose is reduced, recurrent hypoglycemia will develop.

Complications of diabetes that increase the risk for hypoglycemia include autonomic neuropathy, gastroparesis, and end-stage chronic kidney disease. The sympathetic nervous system is an important system alerting the individual that the glucose level is falling by causing symptoms of tachycardia, palpitations, sweating, and tremulousness.

Failure of the sympatho-adrenal responses increases the risk of hypoglycemia. In addition, in patients with gastroparesis, if insulin is given before a meal, the peak of insulin action may occur before the food is absorbed causing the glucose levels to fall. Finally, in end-stage chronic kidney disease, hypoglycemia can occur presumably because of decreased insulin clearance as well as loss of renal contribution to gluconeogenesis in the postabsorptive state.

To prevent and treat insulin-induced hypoglycemia, the diabetic patient should carry glucose tablets or juice at all times. For most episodes, ingestion of 15 grams of carbohydrate is sufficient to reverse the hypoglycemia. The patient should be instructed to check the blood glucose in 15 minutes and treat again if the glucose level is still low. A parenteral (1 mg) or nasal inhalation (3 mg) glucagon emergency kit should be provided to every patient with diabetes who is receiving insulin therapy. Family or friends should be instructed how to inject it subcutaneously or intramuscularly into the buttock, arm, or thigh or administer a nasal dose in the event that the patient is unconscious or refuses food. The medication can occasionally cause vomiting, and the unconscious patient should be turned on his or her side to protect the airway. Glucagon mobilizes glycogen from the liver, raising the blood glucose by about 36 mg/dL (2 mmol/L) in about 15 minutes. After the patient recovers consciousness, additional oral carbohydrate should be given. People with diabetes receiving hypoglycemic medication therapy should also wear an identification MedicAlert bracelet or necklace or carry a card in his or her wallet (1-800-ID-ALERT, www.medicalert.org).

Medical personnel treating severe hypoglycemia can give 50 mL of 50% glucose solution by rapid intravenous infusion. If intravenous access is not available, 1 mg of glucagon can be injected intramuscularly or 3 mg given by nasal spray.

2. Immunopathology of insulin therapy—At least five molecular classes of insulin antibodies are produced during the course of insulin therapy in diabetes, including IgA, IgD, IgE, IgG, and IgM. With the switch to human and purified pork insulin, the various immunopathologic syndromes such as insulin allergy, immune insulin resistance, and lipoatrophy have become quite rare since the titers and avidity of these induced antibodies are generally quite low.

A. INSULIN ALLERGY—Insulin allergy, or immediate-type hypersensitivity, is a rare condition in which local or systemic urticaria is due to histamine release from tissue mast cells sensitized by adherence of anti-insulin IgE antibodies. In severe cases, anaphylaxis results. When only human insulin has been used from the onset of insulin therapy, insulin allergy is exceedingly rare. Antihistamines, corticosteroids, and even desensitization may be required, especially for systemic hypersensitivity.

B. IMMUNE INSULIN RESISTANCE—A low titer of circulating IgG anti-insulin antibodies that neutralize the action of insulin to a small extent develops in most insulin-treated patients. With the old animal insulins, a high titer of circulating antibodies sometimes developed, resulting in

extremely high insulin requirements—often more than 200 units daily. This is now rarely seen with the switch to human or highly purified pork insulins and has not been reported with the analogs.

C. LIPODYSTROPHY—Atrophy of subcutaneous fatty tissue leading to disfiguring excavations and depressed areas may rarely occur at the site of injection. This complication results from an immune reaction, and it has become rarer with the development of human and highly purified insulin preparations. Lipohypertrophy, on the other hand, is a consequence of the pharmacologic effects of insulin being deposited in the same location repeatedly. It can occur with purified insulins as well. Rotation of injection sites will prevent lipohypertrophy.

Rodriguez-Gutierrez R et al. Benefits and harms of intensive glycemic control in patients with type 2 diabetes. *BMJ*. 2019;367:l5887. [PMID: 31690574]

► Chronic Complications of Diabetes

Late clinical manifestations of diabetes mellitus include a number of pathologic changes that involve small and large blood vessels, cranial and peripheral nerves, the skin, and the lens of the eye. These lesions lead to hypertension, end-stage chronic kidney disease, blindness, autonomic and peripheral neuropathy, amputations of the lower extremities, myocardial infarction, and cerebrovascular accidents. These late manifestations correlate with the duration of the diabetic state subsequent to the onset of puberty. In type 1 diabetes, end-stage chronic kidney disease develops in up to 40% of patients, compared with less than 20% of patients with type 2 diabetes. Proliferative retinopathy ultimately develops in both types of diabetes but has a slightly higher prevalence in type 1 patients (25% after 15 years' duration). In patients with type 1 diabetes, complications from end-stage chronic kidney disease are a major cause of death, whereas patients with type 2 diabetes are more likely to have macrovascular diseases leading to myocardial infarction and stroke as the main causes of death. Cigarette use adds significantly to the risk of both microvascular and macrovascular complications in diabetic patients.

A. Ocular Complications

1. Diabetic cataracts—Premature cataracts occur in diabetic patients and seem to correlate with both the duration of diabetes and the severity of chronic hyperglycemia. Nonenzymatic glycosylation of lens protein is twice as high in diabetic patients as in age-matched nondiabetic persons and may contribute to the premature occurrence of cataracts.

2. Diabetic retinopathy—The two main categories of diabetic retinopathy, nonproliferative and proliferative, are discussed in Chapter 7.

3. Glaucoma—Glaucoma occurs in approximately 6% of persons with diabetes. It is responsive to the usual therapy for open-angle disease. Neovascularization of the iris in patients with diabetes can predispose to closed-angle

glaucoma, but this is relatively uncommon except after cataract extraction, when growth of new vessels has been known to progress rapidly, involving the angle of the iris and obstructing outflow.

B. Diabetic Nephropathy

Diabetic nephropathy is initially manifested by albuminuria; subsequently, as kidney function declines, urea and creatinine accumulate in the blood (see Chapter 22). An albumin-creatinine ratio in an early morning spot urine collected upon awakening is the preferred method to assess albumin excretion. In the early morning spot urine, a ratio of albumin (mcg/L) to creatinine (mg/L) of less than 30 mcg/mg creatinine is normal, and a ratio of 30–300 mcg/mg creatinine suggests abnormal microalbuminuria. At least two early morning spot urine collections over a 3- to 6-month period should be abnormal before a diagnosis of microalbuminuria is justified. Short-term hyperglycemia, exercise, urinary tract infections, heart failure, and acute febrile illness can cause transient albuminuria and so testing for microalbuminuria should be postponed until resolution of these problems.

Subsequent end-stage chronic kidney disease can be predicted by persistent urinary albumin excretion rates exceeding 30 mcg/mg creatinine. Glycemic control as well as a protein diet of ~0.8 g/kg/day may reduce both the hyperfiltration and the elevated microalbuminuria in patients in the early stages of diabetes and those with incipient diabetic nephropathy. Antihypertensive therapy also decreases microalbuminuria. Evidence from some studies supports a specific role for ACE inhibitors in reducing intraglomerular pressure in addition to their lowering of systemic hypertension. An ACE inhibitor (captopril, 50 mg twice daily) in normotensive diabetic patients impedes progression to proteinuria and prevents the increase in albumin excretion rate. SGLT2 therapy should be instituted in patients with type 2 diabetes who have progression of kidney disease despite taking optimal antihypertensive therapy, which includes an ACE inhibitor or angiotensin receptor blocker.

C. Diabetic Neuropathy

Diabetic neuropathies are the most common complications of diabetes, affecting up to 50% of older patients with type 2 diabetes.

1. Peripheral neuropathy—

A. DISTAL SYMMETRIC POLYNEUROPATHY—This is the most common form of diabetic peripheral neuropathy where loss of function appears in a stocking-glove pattern and is due to an axonal neuropathic process. Longer nerves are especially vulnerable, hence the impact on the foot. Both motor and sensory nerve conduction is delayed in the peripheral nerves, and ankle jerks may be absent.

Sensory involvement usually occurs first and is generally bilateral, symmetric, and associated with dulled perception of vibration, pain, and temperature. The pain can range from mild discomfort to severe incapacitating symptoms. The sensory deficit may eventually be of sufficient

degree to prevent patients from feeling pain. Patients who have a sensory neuropathy should therefore be examined with a 5.07 Semmes-Weinstein filament and those who cannot feel the filament must be considered at risk for unperceived neuropathic injury.

The denervation of the small muscles of the foot can result in clawing of the toes and displacement of the submetatarsal fat pads anteriorly. These changes, together with the joint and connective tissue changes, alter the biomechanics of the foot and increase plantar pressures. This combination of decreased pain threshold, abnormally high foot pressures, and repetitive stress (such as from walking) can lead to calluses and ulcerations in the high-pressure areas such as over the metatarsal heads (Figure 27–3). Peripheral neuropathy, autonomic neuropathy, and trauma also predisposes to the development of **Charcot arthropathy**. An acute case of Charcot foot arthropathy presents with pain and swelling, and if left untreated, leads to a “rocker bottom” deformity and ulceration. The early radiologic changes show joint subluxation and periarticular fractures. As the process progresses, there is frank osteoclastic destruction leading to deranged and unstable joints particularly in the midfoot. Not surprisingly, the key issue for the healing of neuropathic ulcers in a foot with good vascular supply is mechanical unloading. In addition, any infection should be treated with debridement and appropriate antibiotics; healing duration of 8–10 weeks is typical. Occasionally, when healing appears refractory, platelet-derived growth factor (bepacelmerin [Regranex]) should be considered for local application. Once ulcers are healed, therapeutic footwear is key to preventing recurrences. Custom molded shoes are reserved for patients with significant foot deformities. Other patients with neuropathy may require accommodative insoles that distribute the load over as wide an area as possible. Patients with foot deformities and loss of their protective threshold should get regular care from a podiatrist. Patients should be educated on appropriate footwear and those with loss of their



▲ **Figure 27–3.** Diabetic foot ulcer over head of first metatarsal (arrow). (Used, with permission, from Dean SM, Satiani B, Abraham WT. *Color Atlas and Synopsis of Vascular Diseases*. McGraw-Hill, 2014.)

protective threshold should be instructed to inspect their feet daily for reddened areas, blisters, abrasions, or lacerations.

In some patients, hypersensitivity to light touch and occasionally severe “burning” pain, particularly at night, can become physically and emotionally disabling. Nortriptyline or desipramine in doses of 25–150 mg/day orally may provide dramatic relief for pain from diabetic neuropathy, often within 48–72 hours. Patients often attribute the benefit to having a full night’s sleep. Mild to moderate morning drowsiness is a side effect that generally improves with time or can be lessened by giving the medication several hours before bedtime. This medication should not be continued if improvement has not occurred after 5 days of therapy. Amitriptyline, 25–75 mg orally at bedtime, can also be used but has more anticholinergic effects. Tricyclic antidepressants, in combination with fluphenazine (3 mg daily in three divided doses) have been shown in two studies to be efficacious in painful neuropathy, with benefits unrelated to relief of depression. Gabapentin (900–1800 mg orally daily in three divided doses) has also been shown to be effective in the treatment of painful neuropathy and should be tried if the tricyclic medications prove ineffective. Pregabalin, a congener of gabapentin, has been shown in an 8-week study to be more effective than placebo in treating painful diabetic peripheral neuropathy. However, this medication was not compared with an active control. Also, because of its abuse potential, it has been categorized as a schedule V controlled substance. Duloxetine (60–120 mg), a serotonin and norepinephrine reuptake inhibitor, is approved for the treatment of painful diabetic neuropathy. Capsaicin, a topical irritant, is effective in reducing local nerve pain; it is dispensed as a cream (Zostrix 0.025%, Zostrix-HP 0.075%) to be rubbed into the skin over the painful region two to four times daily. Gloves should be used for application since hand contamination could result in discomfort if the cream comes in contact with eyes or sensitive areas such as the genitalia. Application of a 5% lidocaine patch over an area of maximal pain has been reported to be of benefit. It is approved for treatment of postherpetic neuralgia.

Diabetic neuropathic cachexia is a syndrome characterized by a symmetric peripheral neuropathy associated with profound weight loss (up to 60% of total body weight) and painful dysesthesias affecting the proximal lower limbs, the hands, or the lower trunk. Treatment is usually with insulin and analgesics. The prognosis is generally good, and patients typically recover their baseline weight with resolution of the painful sensory symptoms within 1 year.

B. ISOLATED PERIPHERAL NEUROPATHY—Involvement of the distribution of only one nerve (“mononeuropathy”) or of several nerves (“mononeuropathy multiplex”) is characterized by sudden onset with subsequent recovery of all or most of the function. This neuropathology has been attributed to vascular ischemia or traumatic damage. Cranial and femoral nerves are commonly involved, and motor abnormalities predominate. The patient with cranial nerve involvement usually has diplopia and single third, fourth, or sixth nerve weakness on examination but the pupil is

spared. A full recovery of function occurs in 6–12 weeks. Diabetic amyotrophy presents with onset of severe pain in the front of the thigh. Within a few days or weeks of the onset of pain, weakness and wasting of the quadriceps develops. As the weakness appears, the pain tends to improve. Management includes analgesia and improved diabetes control. The symptoms improve over 6–18 months.

2. Autonomic neuropathy—Neuropathy of the autonomic system occurs principally in patients with diabetes of long duration. It affects many diverse visceral functions including blood pressure and pulse, gastrointestinal activity, bladder function, and erectile dysfunction. Treatment is directed specifically at each abnormality. Insulin neuritis or treatment-induced neuropathy of diabetes occurs occasionally in patients with poor glucose control and whose glucose levels improve rapidly in days or a few weeks. Symptoms include severe sensory neuropathic pains and sometimes autonomic functions. These symptoms improve over a few months.

A. GASTROINTESTINAL SYSTEM—Involvement of the gastrointestinal system may be manifested by nausea, vomiting, postprandial fullness, reflux or dysphagia, constipation or diarrhea (or both), and fecal incontinence. Gastroparesis should be considered in type 1 diabetic patients in whom unexpected fluctuations and variability in their blood glucose levels develops after meals. Metoclopramide has been of some help in treating diabetic gastroparesis. It is given in a dose of 10 mg orally three or four times a day, 30 minutes before meals and at bedtime. Drowsiness, restlessness, fatigue, and lassitude are common adverse effects. Tardive dyskinesia and extrapyramidal effects can occur, especially when used for longer than 3 months, and the FDA has cautioned against the long-term use of metoclopramide.

Erythromycin appears to bind to motilin receptors in the stomach and has been found to improve gastric emptying over the short term in doses of 250 mg three times daily, but its effectiveness seems to diminish over time. In selected patients, injections of botulinum toxin into the pylorus can reduce pylorus sphincter resistance and enhance gastric emptying. Gastric electrical stimulation has been reported to improve symptoms and quality of life indices in patients with gastroparesis refractory to pharmacologic therapy.

Diarrhea associated with autonomic neuropathy has occasionally responded to broad-spectrum antibiotic therapy (such as rifaximin, metronidazole, amoxicillin/clavulanate, ciprofloxacin, or doxycycline), although it often undergoes spontaneous remission. Refractory diabetic diarrhea is often associated with impaired sphincter control and fecal incontinence. Therapy with loperamide, 4–8 mg daily, or diphenoxylate with atropine, two tablets up to four times a day, may provide relief. In more severe cases, tincture of paregoric or codeine (60-mg tablets) may be required to reduce the frequency of diarrhea and improve the consistency of the stools. Clonidine has been reported to lessen diabetic diarrhea; however, its usefulness is limited by its tendency to lower blood pressure in these patients who already have autonomic neuropathy, resulting

in orthostatic hypotension. Constipation usually responds to stimulant laxatives such as senna.

B. GENITOURINARY SYSTEM—Incomplete emptying of the bladder can sometimes occur. Bethanechol in doses of 10–50 mg orally three times a day has occasionally improved emptying of the atonic urinary bladder. Catheter decompression of the distended bladder has been reported to improve its function, and considerable benefit has been reported after surgical severing of the internal vesicle sphincter.

Erectile dysfunction can result from neurologic, psychological, or vascular causes, or a combination of these causes. The phosphodiesterase type 5 (PDE5) inhibitors sildenafil (Viagra), vardenafil (Levitra), and tadalafil (Cialis) have been shown in placebo-controlled clinical trials to improve erections in response to sexual stimulation. The recommended dose of sildenafil for most patients is one 50-mg tablet taken approximately 1 hour before sexual activity. The peak effect is at 1.5–2 hours, with some effect persisting for 4 hours. Patients with diabetes mellitus using sildenafil reported 50–60% improvement in erectile function. The maximum recommended dose is 100 mg. The recommended dose of both vardenafil and tadalafil is 10 mg. The doses may be increased to 20 mg or decreased to 5 mg based on efficacy and side effects. Tadalafil has been shown to improve erectile function for up to 36 hours after dosing. Low doses are available for daily use. In clinical trials, only a few adverse effects have been reported—transient mild headache, flushing, dyspepsia, and some altered color vision. Priapism can occur with these medications, and patients should be advised to seek immediate medical attention if an erection persists for longer than 4 hours. The PDE5 inhibitors potentiate the hypotensive effects of nitrates and their use is contraindicated in patients who are concurrently using organic nitrates in any form. Caution is advised for men who have suffered a heart attack, stroke, or life-threatening arrhythmia within the previous 6 months; men who have resting hypotension or hypertension; and men who have a history of heart failure or have unstable angina. Rarely, a decrease in vision or permanent visual loss has been reported after PDE5 inhibitor use.

Intracorporeal injection of vasoactive medications causes penile engorgement and erection. Medications most commonly used include papaverine alone, papaverine with phentolamine, and alprostadil (prostaglandin E₁). Alprostadil injections are relatively painless, but careful instruction is essential to prevent local trauma, priapism, and fibrosis. Intraurethral pellets of alprostadil avoid the problem of injection of the medication.

External vacuum therapy (Erec-Aid System) is a nonsurgical treatment consisting of a suction chamber operated by a hand pump that creates a vacuum around the penis. This draws blood into the penis to produce an erection that is maintained by a specially designed tension ring inserted around the base of the penis and which can be kept in place for up to 20–30 minutes. While this method is generally effective, its cumbersome nature limits its appeal.

Surgical implants of penile prostheses remain an option for those patients in whom the nonsurgical approaches are ineffective.

C. ORTHOSTATIC HYPOTENSION—Use of Jobst fitted stockings, tilting the head of the bed, and arising slowly from the supine position can be helpful in treating symptoms of orthostatic hypotension. When such measures are inadequate, then treatment with fludrocortisone 0.1–0.2 mg orally daily can be considered. This medication, however, can result in supine hypertension and hypokalemia. The alpha-agonist midodrine (10 mg orally three times a day) can also be used.

D. Cardiovascular Complications

1. Heart disease—Microangiopathy occurs in the heart of patients with diabetes and may explain the etiology of congestive cardiomyopathies in those who do not have demonstrable coronary artery disease. More commonly, however, heart disease in patients with diabetes is due to coronary atherosclerosis. Myocardial infarction is three to five times more common in diabetic patients and is the leading cause of death in patients with type 2 diabetes. Cardiovascular disease risk is increased in patients with type 1 diabetes as well, although the absolute risk is lower than in patients with type 2 diabetes. Premenopausal women who normally have lower rates of coronary artery disease lose this protection once diabetes develops. The increased risk in patients with type 2 diabetes reflects the combination of hyperglycemia, hyperlipidemia, abnormalities of platelet adhesiveness, coagulation factors, hypertension, oxidative stress, and inflammation. Large intervention studies of risk factor reduction in diabetes are lacking, but it is reasonable to assume that reducing these risk factors would have a beneficial effect. Lowering LDL cholesterol reduces first events in patients without known coronary disease and secondary events in patients with known coronary disease. These intervention studies included some patients with diabetes, and the benefits of LDL cholesterol lowering was apparent in this group. The National Cholesterol Education Program clinical practice guidelines have designated diabetes as a coronary risk equivalent and have recommended that patients with diabetes should have an LDL cholesterol goal of less than 100 mg/dL (2.6 mmol/L). Lowering LDL cholesterol to 70 mg/dL (1.8 mmol/L) may have additional benefit and is a reasonable target for most patients with type 2 diabetes who have multiple risk factors for cardiovascular disease.

Aspirin at a dose of 81–325 mg daily is effective in reducing cardiovascular morbidity and mortality in patients who have a history of myocardial infarction or stroke (secondary prevention). For primary prevention, a 2018 randomized study of 15,480 persons with diabetes but no evident cardiovascular disease observed that 100 mg of aspirin reduced the first vascular event of myocardial infarction, stroke or transient ischemic attack or death from vascular event (excluding intracranial hemorrhage) (rate ratio 0.88; 95% confidence interval 0.79 to 0.97). There were, however, more major bleeding events, especially gastrointestinal, in the aspirin group (rate ratio 1.29; 95% confidence interval 1.09 to 1.52). Thus, for primary prevention, the use of aspirin should only be considered for patients with high cardiovascular risk and low bleeding risk and generally not for adults older than 70 years. Based

on the Early Treatment Diabetic Retinopathy Study (ETDRS), there does not appear to be a contraindication to aspirin use to achieve cardiovascular benefit in diabetic patients who have proliferative retinopathy. Aspirin also does not seem to affect the severity of vitreous/preretinal hemorrhages or their resolution.

2. Hypertension—The ADA recommends lowering systolic blood pressure to less than 140 mm Hg and diastolic pressure to less than 90 mm Hg in patients with diabetes. The systolic target of 130 mm Hg or less and diastolic target of 80 mm Hg or less are recommended for the younger patient if they can be achieved without undue treatment burden. The Systolic Blood Pressure Intervention Trial (SPRINT) reported that treating to a systolic blood pressure of less than 120 mm Hg reduced cardiovascular events by 25% and death from cardiovascular causes by 43% during 3.26 years of follow-up. People with diabetes, however, were excluded from this study, and it is unclear if the results are applicable to this population. Patients with type 2 diabetes who already have cardiovascular disease or microalbuminuria should be considered for treatment with an ACE inhibitor. More clinical studies are needed to address the question of whether patients with type 2 diabetes who do not have cardiovascular disease or microalbuminuria would specifically benefit from ACE inhibitor treatment.

3. Peripheral vascular disease—Atherosclerosis is markedly accelerated in the larger arteries. It is often diffuse, with localized enhancement in certain areas of turbulent blood flow, such as at the bifurcation of the aorta or other large vessels. Clinical manifestations of peripheral vascular disease include ischemia of the lower extremities, erectile dysfunction, and intestinal angina.

The incidence of **gangrene of the feet** in patients with diabetes is 30 times that in age-matched controls. The factors responsible for its development, in addition to peripheral vascular disease, are small vessel disease, peripheral neuropathy with loss of both pain sensation and neurogenic inflammatory responses, and secondary infection. In two-thirds of patients with ischemic gangrene, pedal pulses are not palpable. In the remaining one-third who have palpable pulses, reduced blood flow through these vessels can be demonstrated by plethysmographic or Doppler ultrasound examination. Prevention of foot injury is imperative. Agents that reduce peripheral blood flow such as tobacco should be avoided. Control of other risk factors such as hypertension is essential. Beta-blockers are relatively contraindicated because of presumed negative peripheral hemodynamic consequences but data that support this are lacking. Cholesterol-lowering agents are useful as adjunctive therapy when early ischemic signs are detected and when dyslipidemia is present. Patients should be advised to seek immediate medical care if a diabetic foot ulcer develops. Improvement in peripheral blood flow with endarterectomy and bypass operations is possible in certain patients.

E. Skin and Mucous Membrane Complications

Chronic pyogenic infections of the skin may occur, especially in poorly controlled diabetic patients. Candidal

infection can produce erythema and edema of intertriginous areas below the breasts, in the axillas, and between the fingers. It causes vulvovaginitis in women with chronically uncontrolled diabetes who have persistent glucosuria and is a frequent cause of pruritus. While antifungal creams containing miconazole or clotrimazole offer immediate relief of vulvovaginitis, recurrence is frequent unless glucosuria is reduced.

In some patients with type 2 diabetes, poor glycemic control can cause severe hypertriglycerolemia, which can present as eruptive cutaneous xanthomas and pancreatitis. The skin lesions appear as yellow morbilliform eruptions 2–5 mm in diameter with erythematous areolae. They occur on extensor surfaces (elbows, knees, buttocks) and disappear after triglyceride levels are reduced.

Necrobiosis lipoidica diabetorum is usually located over the anterior surfaces of the legs or the dorsal surfaces of the ankles. They are oval or irregularly shaped plaques with demarcated borders and a glistening yellow surface and occur in women two to four times more frequently than in men. Pathologically, the lesions show degeneration of collagen, granulomatous inflammation of subcutaneous tissues and blood vessels, capillary basement membrane thickening and obliteration of vessel lumina. The condition is associated with type 1 diabetes, although it can occur in patients with type 2 diabetes, and also in patients without diabetes. First-line therapy includes topical and subcutaneous corticosteroids. Improving glycemic control may help the condition.

“Shin spots” are not uncommon in adults with diabetes. They are brownish, rounded, painless atrophic lesions of the skin in the pretibial area.

F. Bone and Joint Complications

Long-standing diabetes can cause progressive stiffness of the hand secondary to contracture and tightening of skin over the joints (diabetic cheiroarthropathy), frozen shoulder (adhesive capsulitis), carpal tunnel syndrome, and Dupuytren contractures. These complications are believed to be due to glycosylation of collagen and perhaps other proteins in connective tissue. There may also be an inflammatory component.

Data on bone mineral density and fracture risk in people with diabetes are contradictory. Patients with type 2 diabetes do appear to be at increased risk for nonvertebral fractures. Women with type 1 diabetes have an increased risk of fracture when compared with women without diabetes. Other factors, such as duration of diabetes, and diabetes complications, such as neuropathy and kidney disease, likely affect both the bone mineral density and fracture risk.

Diffuse idiopathic skeletal hyperostosis (DISH) is characterized by ossification of the anterior longitudinal ligaments of the spine and various extraspinal ligaments. It causes stiffness and decreased range of spinal motion. The peripheral joints most commonly affected are the metacarpophalangeal joints, elbows, and shoulders. Diabetes, obesity, hypertension, and dyslipidemia are risk factors for this condition.

Hyperuricemia and acute and tophaceous gout are more common in type 2 diabetes.

Bursitis, particularly of the shoulders and hips, occurs more frequently than expected in patients with diabetes.

- ASCEND Study Collaborative Group et al. Effects of aspirin for primary prevention in persons with diabetes mellitus. *N Engl J Med.* 2018;379:1529. [PMID: 30146931]
- Grennan D. Diabetic foot ulcers. *JAMA.* 2019;321:114. [PMID: 30620372]
- Hinchliffe RJ et al; International Working Group on the Diabetic Foot (IWGDF). Guidelines on diagnosis, prognosis, and management of peripheral artery disease in patients with foot ulcers and diabetes (IWGDF 2019 update). *Diabetes Metab Res Rev.* 2020;36:e3276. [PMID: 31958217]
- Selvarajah D et al. Diabetic peripheral neuropathy: advances in diagnosis and strategies for screening and early intervention. *Lancet Diabetes Endocrinol.* 2019;7:938. [PMID: 31624024]
- Shen JI et al. Evidence for and against ACC/AHA 2017 guideline for target systolic blood pressure of < 130 mm Hg in persons with type 2 diabetes. *Curr Cardiol Rep.* 2019;21:149. [PMID: 31760494]

► Special Situations

A. Diabetes Management in the Hospital

Hospitalized patients are generally not eating as usual and they are often fasting for procedures, which makes it challenging to use outpatient oral or insulin regimens. There may be an increase in the adverse reactions of diabetes medicines (eg, thiazolidinediones can cause fluid retention and worsen heart failure); metformin should not be used in patients with significant chronic kidney or liver disease or those getting contrast for radiographic studies; and SGLT2 inhibitors may be associated with increased risk of diabetic ketoacidosis. The data on the use of continuous glucose monitors, insulin pumps, and hybrid closed loop systems in hospitalized patients are insufficient. Whether patients stay on these systems in the hospital will depend on their severity of illness and access to specialist care. In general, decisions regarding insulin dosing should be made based on capillary blood glucose measurements and not on the data from continuous glucose monitors. Patients should be transitioned to a conventional basal bolus subcutaneous insulin regimen if they are unable to manage their pump and/or continuous glucose monitor because of their illness or if they refuse to follow the institutional guidelines on using the pump or continuous monitor (eg, giving themselves insulin boluses and not informing the clinical staff). The systems have to be removed if the patient is getting an MRI.

On the **general medical and surgical inpatient services**, most patients are treated with subcutaneous insulin regimens. Limited cross-sectional and prospective studies suggest that the best glucose control is achieved on a combination of basal and bolus regimen with 50% of daily insulin needs provided by intermediate- or long-acting insulins. Standardized order sets can reduce errors, and they often include algorithms for recognition and treatment of hypoglycemia (see <http://ucsfpatientdiabetes.pbworks.com> for examples). Oral medicines, especially metformin and sulfonylureas, can be resumed as the patient is being prepared for hospital discharge.

In the **intensive care units (ICUs)**, glucose levels are controlled most frequently using insulin infusions

(<http://ucsfpatientdiabetes.pbworks.com>). Patients receiving total parenteral nutrition can have insulin added to the bag. Standard total parenteral nutrition contains 25% dextrose so an infusion rate of 50 mL/h delivers 12.5 g of dextrose per hour.

Based on the evidence available, ICU patients with diabetes and new-onset hyperglycemia with blood glucose levels above 180 mg/dL (10 mmol/L) should be treated with insulin, aiming for target glucose levels between 140 mg/dL (7.8 mmol/L) and 180 mg/dL (10 mmol/L). In the ICU setting, aiming for blood glucose levels close to 100 mg/dL (5.6 mmol/L) is not beneficial and may even be harmful. When patients leave the ICU, target glucose values between 100 mg/dL (5.6 mmol/L) and 180 mg/dL (10 mmol/L) may be appropriate, although this view is based on clinical observations rather than conclusive evidence.

Preoperative and perioperative diabetic management strategies are discussed in Chapter 3.

The morbidity and mortality in hospitalized diabetic patients are twice those of nondiabetic patients. Those with new-onset hyperglycemia (ie, those without a preadmission diagnosis of diabetes) have even higher mortality—almost eightfold that of nondiabetic patients in one study. These observations have led to the question of whether tight glycemic control in the hospital improves outcomes.

B. Pregnancy and the Diabetic Patient

See Chapter 19. Tight glycemic control with normal HbA_{1c} levels is very important during pregnancy. Early in pregnancy, poor control increases the risk of spontaneous abortion and congenital malformations. Late in pregnancy, poor control can result in polyhydramnios, preterm labor, stillbirth, and fetal macrosomia with its associated problems. Diabetes complications can impact both maternal and fetal health. Diabetic retinopathy can first develop during pregnancy or retinopathy that is already present can worsen. Diabetic women with microalbuminuria can have worsening albuminuria during pregnancy and are at higher risk for preeclampsia. Low-dose (81 mg) aspirin can reduce the risk of preeclampsia and should be prescribed after 12 weeks of gestation. Patients who have preexisting kidney failure (pregnancy creatinine clearance less than 80 mL/min) are at high risk for further decline in kidney function during the pregnancy, and this may not reverse after delivery. Diabetic gastroparesis can severely exacerbate the nausea and vomiting of pregnancy and some patients may require fluid and nutritional support.

Although there is evidence that glyburide is safe during pregnancy, the current practice is to control diabetes with insulin therapy. Every effort should be made, utilizing multiple injections of insulin or a continuous infusion of insulin by pump, to maintain near-normalization of fasting and preprandial blood glucose values while avoiding hypoglycemia.

Regular and NPH insulin and the insulin analogs lispro, aspart, and detemir are labeled pregnancy category B. Insulin glargine, glulisine, and degludec are labeled category C because of lack of clinical safety data. A small study using insulin glargine in 32 pregnancies did not reveal any problems.

Table 27–10. Laboratory diagnosis of coma in diabetic patients.

	Urine Glucose	Urine Ketones	Plasma Glucose	Serum Bicarbonate	Serum Ketones
Related to Diabetes					
Hypoglycemia	0 ¹	0 or +	Low	Normal	0
Diabetic ketoacidosis	++++	++++	High	Low	++++
Hyperglycemic hyperosmolar state coma	++++	0 or +	High	Normal or slightly low	0
Lactic acidosis	0 or +	0 or +	Normal or low or high	Low	0 or +
Unrelated to Diabetes					
Alcohol or other toxic drugs	0 or +	0 or +	May be low	Normal or low ²	0 or +
Cerebrovascular accident or head trauma	+ or 0	0	Often high	Normal	0
Uremia	0 or +	0	High or normal	Low	0 or +

¹Leftover urine in bladder might still contain glucose from earlier hyperglycemia.

²Alcohol can elevate plasma lactate as well as keto acids to reduce pH.

Unless there are fetal or maternal complications, diabetic women should be able to carry the pregnancy to full-term, delivering at 38 to 41 weeks. Induction of labor before 39 weeks may be considered if there is concern about increasing fetal weight. See Chapter 19 for further details.

American Diabetes Association. Management of diabetes in pregnancy: *Standards of Medical Care in Diabetes—2020*. Diabetes Care. 2020;43:S183. [PMID: 31862757]

DIABETIC COMA

Coma may be due to causes not directly related to diabetes. Diabetic coma requires differentiation (Table 27–10): (1) Hypoglycemic coma from excessive insulin or oral hypoglycemic agents. (2) Hyperglycemic coma with either severe insulin deficiency (DKA) or mild to moderate insulin deficiency (hyperglycemic hyperosmolar state). (3) Lactic acidosis, particularly when patients with diabetes have severe infections or cardiovascular collapse.

DIABETIC KETOACIDOSIS



ESSENTIALS OF DIAGNOSIS

- ▶ Hyperglycemia > than 250 mg/dL (13.9 mmol/L).
- ▶ Metabolic acidosis with blood pH < 7.3; serum bicarbonate < 15 mEq/L.
- ▶ Serum positive for ketones.

► General Considerations

Diabetic ketoacidosis (DKA) is a disorder primarily in patients with type 1 diabetes but can occur in patients with type 2 diabetes who have severe illness, such as sepsis or trauma. DKA may be the initial manifestation of type 1

diabetes or may result from increased insulin requirements in type 1 diabetes patients during the course of infection, trauma, myocardial infarction, or surgery. It is a life-threatening medical emergency. The National Data Group reports an annual incidence of five to eight episodes of DKA per 1000 diabetic persons. DKA is one of the more common serious complications of insulin pump therapy, occurring in approximately 1 per 80 patient-months of treatment. Many patients who monitor capillary blood glucose regularly ignore urine ketone measurements, which signals the possibility of insulin leakage or pump failure before serious illness develops. Poor compliance, either for psychological reasons or because of inadequate education, is one of the most common causes of recurrent DKA.

► Clinical Findings

A. Symptoms and Signs

The appearance of DKA is usually preceded by a day or more of polyuria and polydipsia associated with marked fatigue, nausea, and vomiting.

If untreated, mental stupor ensues that can progress to coma. Drowsiness is fairly common, but frank coma only occurs in about 10% of patients. On physical examination, evidence of dehydration in a stuporous patient with rapid deep breathing and a “fruity” breath odor of acetone strongly suggests the diagnosis. Hypotension with tachycardia indicates profound fluid and electrolyte depletion, and mild hypothermia is usually present. Abdominal pain and even tenderness may be present in the absence of abdominal disease. Conversely, cholecystitis or pancreatitis may occur with minimal symptoms and signs.

B. Laboratory Findings

Typically, the patient with moderately severe DKA has a plasma glucose of 350–900 mg/dL (19.4–50 mmol/L), serum ketones at a dilution of 1:8 or greater or

beta-hydroxybutyrate more than 4 nmol/L, hyperkalemia (serum potassium level of 5–8 mEq/L), mild hyponatremia (serum sodium of approximately 130 mEq/L), hyperphosphatemia (serum phosphate level of 6–7 mg/dL [1.9–2.3 mmol/L]), and elevated blood urea nitrogen and serum creatinine levels (Table 27–10). Acidosis may be severe (pH ranging from 6.9 to 7.2 and serum bicarbonate ranging from 5 mEq/L to 15 mEq/L); PCO_2 is low (15–20 mm Hg) related to compensatory hyperventilation. Fluid depletion is marked, typically about 100 mL/kg. In euglycemic ketoacidosis, the patient can have severe acidosis and fluid depletion but the plasma glucose levels are only modestly elevated, usually less than 250 mg/day (13.9 mmol/L). This condition is seen in patients in whom diabetic ketoacidosis develops while receiving treatment with SGLT2 inhibitors. Ketoacidosis with lower glucose levels also occurs in pregnancy and may reflect the expanded plasma volume and the increased glomerular filtration rate.

The difference between venous and arterial pH is 0.02 to 0.15 pH units and venous and arterial bicarbonate is 1.88 mEq/L. These small differences will not affect either the diagnosis or the management of DKA, and there is no need to collect arterial blood for measuring the acid-base status.

The hyperkalemia occurs despite total body potassium depletion because of the shift of potassium from the intracellular to extracellular spaces that occurs in systemic acidosis. The average total body potassium deficit resulting from osmotic diuresis, acidosis, and gastrointestinal losses is about 3–5 mEq/kg. Similarly, despite the elevated serum phosphate, total body phosphate is generally depleted. Serum sodium is generally reduced due to loss of sodium ions (7–10 mEq/kg) by polyuria and vomiting and because severe hyperglycemia shifts intracellular water into the interstitial compartment. For every 100 mg/dL of plasma glucose, serum sodium decreases by 1.6 mEq/L (5.56 mmol/L). The decrease in serum sodium may be greater when patients have more severe hyperglycemia (greater than 400 mg/dL, 22.2 mmol/L) and a correction factor of 2.4 mEq/L may be used. Hypertriglyceridemia should be considered if the corrected sodium is very low. Serum osmolality can be directly measured by standard tests of freezing point depression or can be estimated by calculating the molarity of sodium, chloride, and glucose in the serum. A convenient method of estimating effective serum osmolality is as follows (normal values are 280–300 mOsm/kg):

$$\text{mOsm/kg} = 2 [\text{measured Na}^+] + \frac{\text{Glucose (mg/dL)}}{18}$$

These calculated estimates are usually 10–20 mOsm/kg lower than values measured by standard cryoscopic techniques. Central nervous system depression or coma occurs when the effective serum osmolality exceeds 320–330 mOsm/L. Coma in a diabetic patient with a lower osmolality should prompt a search for the cause of coma other than hyperosmolality (see Table 27–10 and Chapter 24).

Ketoacidemia represents the effect of insulin lack at multiple enzyme loci. Insulin lack associated with elevated levels of growth hormone, catecholamines, and glucagon contributes to increases in lipolysis from adipose tissue and in hepatic ketogenesis. In addition, reduced ketolysis by insulin-deficient peripheral tissues contributes to the ketoacidemia. The only true “keto” acid present in diabetic ketoacidosis is acetoacetic acid which, along with its by-product acetone, is measured by nitroprusside reagents (Acetest and Ketostix). The sensitivity for acetone, however, is poor, requiring over 10 mmol/L, which is seldom reached in the plasma of ketoacidotic patients—although this detectable concentration is readily achieved in urine. Thus, in the plasma of ketotic patients, only acetoacetate is measured by these reagents. The more prevalent beta-hydroxybutyric acid has no ketone group and is therefore not detected by conventional nitroprusside tests. This takes on special importance in the presence of circulatory collapse during DKA, wherein an increase in lactic acid can shift the redox state to increase beta-hydroxybutyric acid at the expense of the readily detectable acetoacetic acid. Bedside diagnostic reagents are then unreliable, suggesting no ketonemia in cases where beta-hydroxybutyric acid is a major factor in producing the acidosis. Combined glucose and ketone meters (Precision Xtra, Nova Max Plus) that measure blood beta-hydroxybutyrate concentration on capillary blood are available. Many clinical laboratories also offer direct blood beta-hydroxybutyrate measurement.

Nonspecific elevations of serum amylase and lipase occurs in about 16–25% of cases of DKA, and an imaging study may be necessary if the diagnosis of acute pancreatitis is being seriously considered. Leukocytosis as high as 25,000/mcL ($25 \times 10^9/\text{L}$) with a left shift may occur with or without associated infection. The presence of an elevated or even a normal temperature can suggest the presence of an infection since patients with DKA are generally hypothermic if uninfected.

► Treatment

Patients with **mild DKA** are alert and have pH levels between 7.25 and 7.30 and beta-hydroxybutyrate levels of 3–4 mmol/L; those with **moderate ketoacidosis** are either alert or a little drowsy and have pH levels between 7.0 and 7.24 and beta-hydroxybutyrate levels of 4–8 mmol/L; and those with **severe ketoacidosis** are stuporose and have a pH < 7.0 and beta-hydroxybutyrate levels of greater than 8 mmol/L. Patients with mild ketoacidosis can be treated in the emergency department, but those with moderate or severe ketoacidosis require admission to the ICU or step-down unit. Therapeutic goals are to restore plasma volume and tissue perfusion, reduce blood glucose and osmolality toward normal, correct acidosis, replenish electrolyte losses, and identify and treat precipitating factors. Gastric intubation is recommended in the comatose patient to prevent vomiting and aspiration that may occur as a result of gastric atony, a common complication of DKA. An indwelling urinary catheter may also be necessary. In patients with preexisting heart or kidney failure or those in severe cardiovascular collapse, a central venous pressure

catheter should be inserted to evaluate the degree of hypovolemia and to monitor subsequent fluid administration.

A comprehensive flow sheet that includes vital signs, serial laboratory data, and therapeutic interventions (eg, fluids, insulin) should be meticulously maintained by the clinician responsible for the patient's care. Plasma glucose should be recorded hourly and electrolytes and pH at least every 2–3 hours during the initial treatment period. Bedside glucose meters should be used to titrate the insulin therapy. The patient should not receive sedatives or opioids in order to avoid masking signs and symptoms of impeding cerebral edema.

A. Fluid Replacement

In most patients, the fluid deficit is 4–5 L. Initially, 0.9% saline solution is the solution of choice to help reexpand the contracted vascular volume and should be started in the emergency department as soon as the diagnosis is established. The saline should be infused rapidly to provide 1 L/h over the first 1–2 hours. After the first 2 L of fluid have been given, the intravenous infusion should be at the rate of 300–400 mL/h. Use 0.9% ("normal") saline unless the serum sodium is greater than 150 mEq/L, when 0.45% ("half normal") saline solution should be used. The volume status should be carefully monitored clinically. Failure to give enough volume replacement (at least 3–4 L in 8 hours) to restore normal perfusion is one of the most serious therapeutic shortcomings adversely influencing satisfactory recovery. Excessive fluid replacement (more than 5 L in 8 hours) may contribute to acute respiratory distress syndrome or cerebral edema. When blood glucose falls to approximately 250 mg/dL (13.9 mmol/L), the fluids should be changed to a 5% glucose-containing solution to maintain serum glucose in the range of 250–300 mg/dL (13.9–16.7 mmol/L). This will prevent the development of hypoglycemia and will also reduce the likelihood of cerebral edema, which could result from too rapid decline of blood glucose.

B. Insulin Replacement

Immediately after initiation of fluid replacement, regular insulin can be given intravenously in a loading dose of 0.1 unit/kg as a bolus to prime the tissue insulin receptors. Following the initial bolus, intravenous doses of insulin as low as 0.1 unit/kg/h are continuously infused or given hourly as an intramuscular injection; this is sufficient to replace the insulin deficit in most patients. A prospective randomized study showed that a bolus dose is not required if patients are given hourly insulin infusion at 0.14 unit/kg. Replacement of insulin deficiency helps correct the acidosis by reducing the flux of fatty acids to the liver, reducing ketone production by the liver, and also improving removal of ketones from the blood. Insulin treatment reduces the hyperosmolality by reducing the hyperglycemia. It accomplishes this by increasing removal of glucose through peripheral utilization as well as by decreasing production of glucose by the liver. This latter effect is accomplished by direct inhibition of gluconeogenesis and glycogenolysis as

well as by lowered amino acid flux from muscle to liver and reduced hyperglucagonemia.

The insulin infusion should be "piggy-backed" into the fluid line so the rate of fluid replacement can be changed without altering the insulin delivery rate. If the plasma glucose level fails to fall at least 10% in the first hour, a repeat loading dose (0.1 or 0.14 unit/kg) is recommended. Rarely, a patient with immune insulin resistance is encountered, and this requires doubling the insulin dose every 2–4 hours if hyperglycemia does not improve after the first two doses of insulin. The insulin dose should be adjusted to lower the glucose concentration by about 50–70 mg/dL/h (2.8–3.9 mmol/L). If clinical circumstances prevent use of an insulin infusion, then the insulin can be given intramuscularly. An initial 0.15 unit/kg of regular insulin is given intravenously, and at the same time, the same size dose is given intramuscularly. Subsequently, regular insulin is given intramuscularly hourly at a dose of 0.1 unit/kg until the blood glucose falls to around 250 mg/dL, when the insulin can be given subcutaneously. Patients who normally take insulin glargine or insulin detemir can be given their usual maintenance doses during the initial treatment of their DKA. The continuation of their subcutaneous basal insulins means that lower doses of intravenous insulin will be needed, and there will be a smoother transition from intravenous insulin infusion to the subcutaneous regimen.

C. Potassium

Total body potassium loss from polyuria and vomiting may be as high as 200 mEq. However, because of shifts of potassium from cells into the extracellular space as a consequence of acidosis, serum potassium is usually normal to slightly elevated prior to institution of treatment. As the acidosis is corrected, potassium flows back into the cells, and hypokalemia can develop if potassium replacement is not instituted. If the patient is not uremic and has an adequate urinary output, potassium chloride in doses of 10–30 mEq/h should be infused during the second and third hours after beginning therapy as soon as the acidosis starts to resolve. Replacement should be started sooner if the initial serum potassium is inappropriately normal or low and should be delayed if serum potassium fails to respond to initial therapy and remains above 5 mEq/L, as in cases of chronic kidney disease. Occasionally, a patient may present with a serum potassium level less than 3.5 mEq/L, in which case insulin therapy should be delayed until the potassium level is corrected to greater than 3.5 mEq/L. An ECG can help monitor the patient's potassium status: High peaked T waves are a sign of hyperkalemia, and flattened T waves with U waves are a sign of hypokalemia. Foods high in potassium content should be prescribed when the patient has recovered sufficiently to take food orally. Tomato juice has 14 mEq of potassium per 240 mL, and a medium-sized banana provides about 10 mEq.

D. Sodium Bicarbonate

The use of sodium bicarbonate in the management of DKA has been questioned since clinical benefit was not

demonstrated in one prospective randomized trial and because of the following potentially harmful consequences: (1) development of hypokalemia from rapid shift of potassium into cells if the acidosis is overcorrected; (2) tissue anoxia from reduced dissociation of oxygen from hemoglobin when acidosis is rapidly reversed (leftward shift of the oxygen dissociation curve); and (3) cerebral acidosis resulting from lowering of cerebrospinal fluid pH. It must be emphasized, however, that these considerations are less important when very severe acidosis exists. Therefore, it is recommended that bicarbonate be administered in DKA if the arterial blood pH is 7.0 or less, with careful monitoring to prevent overcorrection. One or two ampules of sodium bicarbonate (one ampule contains 44 mEq/50 mL) should be added to 1 L of 0.45% saline with 20 mEq KCl or to 400 mL of sterile water with 20 mEq KCl and infused over 1 to 2 hours. (**Note:** Addition of sodium bicarbonate to 0.9% saline would produce a markedly hypertonic solution that could aggravate the hyperosmolar state already present.) It can be repeated until the arterial pH reaches 7.1, but *it should not be given if the pH is 7.1 or greater* since additional bicarbonate would increase the risk of rebound metabolic alkalosis as ketones are metabolized. Alkalosis shifts potassium from serum into cells, which could precipitate a fatal cardiac arrhythmia.

E. Phosphate

Phosphate replacement is seldom required in treating DKA. However, if severe hypophosphatemia of less than 1 mg/dL (0.32 mmol/L) develops during insulin therapy, a small amount of phosphate can be replaced per hour as the potassium salt. Three randomized studies, though, in which phosphate was replaced in patients with DKA did not show any apparent clinical benefit from phosphate administration. Moreover, attempts to use potassium phosphate as the sole means of replacing potassium have led to a number of reported cases of severe hypocalcemia with tetany. To minimize the risk of inducing tetany from too-rapid replacement of phosphate, the average deficit of 40–50 mmol of phosphate should be replaced intravenously at a rate *no greater than 3–4 mmol/h* in a 60- to 70-kg person. A stock solution (Abbott) provides a mixture of 1.12 g KH₂PO₄ and 1.18 g K₂HPO₄ in a 5-mL single-dose vial (this equals 22 mmol of potassium and 15 mmol of phosphate). One-half of this vial (2.5 mL) should be added to 1 L of either 0.45% saline or 5% dextrose in water. Two liters of this solution, infused at a rate of 400 mL/h, will correct the phosphate deficit at the optimal rate of 3 mmol/h while providing 4.4 mEq of potassium per hour. (Additional potassium should be administered as potassium chloride to provide a total of 10–30 mEq of potassium per hour, as noted above.) If the serum phosphate remains below 2.5 mg/dL (0.8 mmol/L) after this infusion, a repeat 5-hour infusion can be given.

F. Hyperchloremic Acidosis During Therapy

Because of the considerable loss of keto acids in the urine during the initial phase of therapy, substrate for subsequent regeneration of bicarbonate is lost and correction of the total bicarbonate deficit is hampered. A portion of the

bicarbonate deficit is replaced with chloride ions infused in large amounts as saline to correct the dehydration. In most patients, as the ketoacidosis clears during insulin replacement, a hyperchloremic, low-bicarbonate pattern emerges with a normal anion gap. This is a relatively benign condition that reverses itself over the subsequent 12–24 hours once intravenous saline is no longer being administered. Using a balanced electrolyte solution with a pH of 7.4 and 98 mEq/L chloride such as Plasma-lyte instead of normal saline (pH ~5.5; chloride 154 mEq/L) has been reported to prevent the hyperchloremic acidosis.

G. Treatment of Associated Infection

Antibiotics are prescribed as indicated (Table 30–5). Cholecystitis and pyelonephritis may be particularly severe in these patients.

H. Transition to Subcutaneous Insulin Regimen

Once the DKA is controlled and the patient is awake and able to eat, subcutaneous insulin therapy can be initiated. The patient with type 1 diabetes may have persistent significant tissue insulin resistance and may require a total daily insulin dose of approximately 0.6 unit/kg. The amount of insulin required in the previous 8 hours can also be helpful in estimating the initial insulin doses. Half the total daily dose can be given as a long-acting basal insulin and the other half as short-acting insulin premeals. The patient should receive subcutaneous basal insulin and rapid-acting insulin analog with the first meal and the insulin infusion discontinued an hour later. The overlap of the subcutaneous insulin action and insulin infusion is necessary to prevent relapse of the DKA. In patients with preexisting diabetes, giving their basal insulin by subcutaneous injection at initiation of treatment simplifies the transition from intravenous to subcutaneous regimen. The increased insulin resistance is only present for a few days, and it is important to reduce both the basal and bolus insulins to avoid hypoglycemia. A patient with new-onset type 1 diabetes usually still has significant beta cell function and may not need any basal insulin and only very low doses of rapid-acting insulin before meals after recovery from the ketoacidosis. Patients with type 2 diabetes and DKA due to severe illness may initially require insulin therapy but can often transition back to oral agents during outpatient follow-up.

► Complications & Prognosis

Low-dose insulin infusion and fluid and electrolyte replacement combined with careful monitoring of patients' clinical and laboratory responses to therapy have dramatically reduced the mortality rates of DKA to less than 5% in individuals under 40 years of age. However, this complication remains a significant risk in the aged who have mortality rates greater than 20% and in patients in profound coma in whom treatment has been delayed. Acute myocardial infarction and infarction of the bowel following prolonged hypotension worsen the outlook. A serious prognostic sign is end-stage chronic kidney disease, and prior kidney dysfunction worsens the prognosis considerably because the kidney plays a key role in compensating

for massive pH and electrolyte abnormalities. Symptomatic cerebral edema occurs primarily in the pediatric population. Risk factors for its development include severe baseline acidosis, rapid correction of hyperglycemia, and excess volume administration in the first 4 hours. Onset of headache or deterioration in mental status during treatment should lead to consideration of this complication. Intravenous mannitol at a dosage of 1–2 g/kg given over 15 minutes is the mainstay of treatment. Excess crystalloid infusion can precipitate pulmonary edema. Acute respiratory distress syndrome is a rare complication of treatment of DKA.

After recovery and stabilization, patients should be instructed on how to recognize the early symptoms and signs of ketoacidosis. Urine ketones or capillary blood beta-hydroxybutyrate should be measured in patients with signs of infection or in insulin pump-treated patients when capillary blood glucose remains unexpectedly and persistently high. When heavy ketonuria and glycosuria persist on several successive examinations, supplemental rapid-acting insulin should be administered and liquid foods such as lightly salted tomato juice and broth should be ingested to replenish fluids and electrolytes. The patient should be instructed to contact the clinician if ketonuria persists, and especially if there is vomiting and inability to keep down fluids. Recurrent episodes of severe ketoacidosis often indicate poor compliance with the insulin regimen, and these patients will require intensive counseling.

Fayman M et al. Management of hyperglycemic crises: diabetic ketoacidosis and hyperglycemic hyperosmolar state. *Med Clin North Am.* 2017;101:587. [PMID: 28372715]

Islam T et al. Guidelines and controversies in the management of diabetic ketoacidosis—a mini-review. *World J Diabetes.* 2018;9:226. [PMID: 30588284]

Karslioglu French E et al. Diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome: review of acute decompensated diabetes in adult patients. *BMJ.* 2019;365:l114. [PMID: 31142480]

Modi A et al. Euglycemic diabetic ketoacidosis: a review. *Curr Diabetes Rev.* 2017;13:315. [PMID: 27097605]

patients are typically middle-aged to elderly. Accurate figures are not available as to its true incidence, but from data on hospital discharges it is rarer than DKA even in older age groups. Underlying chronic kidney disease or heart failure is common, and the presence of either worsens the prognosis. A precipitating event such as infection, myocardial infarction, stroke, or recent operation is often present. Certain medications such as phenytoin, diazoxide, corticosteroids, and diuretics have been implicated in its pathogenesis, as have procedures associated with glucose loading such as peritoneal dialysis.

► Pathogenesis

A partial or relative insulin deficiency may initiate the syndrome by reducing glucose utilization of muscle, fat, and liver while inducing hyperglucagonemia and increasing hepatic glucose output. With massive glycosuria, obligatory water loss ensues. If a patient is unable to maintain adequate fluid intake because of an associated acute or chronic illness or has suffered excessive fluid loss, marked dehydration results. As the plasma volume contracts, kidney function becomes impaired, limiting the urinary glucose losses and exacerbating the hyperglycemia. Severe hyperosmolality develops that causes mental confusion and finally coma. It is not clear why ketosis is virtually absent under these conditions of insulin insufficiency, although reduced levels of growth hormone may be a factor, along with portal vein insulin concentrations sufficient to restrain ketogenesis.

► Clinical Findings

A. Symptoms and Signs

Onset may be insidious over a period of days or weeks, with weakness, polyuria, and polydipsia. The lack of features of DKA (eg, vomiting, rapid deep breathing, acetone odor) may retard recognition of the syndrome and delay therapy until dehydration becomes more profound than in ketoacidosis. Reduced intake of fluid is not an uncommon historical feature, due to either inappropriate lack of thirst, nausea, or inaccessibility of fluids to elderly, bedridden patients. A history of ingestion of large quantities of glucose-containing fluids, such as soft drinks or orange juice, can occasionally be obtained. Lethargy and confusion develop as serum osmolality exceeds 310 mOsm/kg, and convulsions and coma can occur if osmolality exceeds 320–330 mOsm/kg. Physical examination confirms the presence of profound dehydration in a lethargic or comatose patient without Kussmaul respirations.

B. Laboratory Findings

Severe hyperglycemia is present, with blood glucose values ranging from 800 mg/dL to 2400 mg/dL (44.4 mmol/L to 133.2 mmol/L) (Table 27–10). In mild cases, where dehydration is less severe, dilutional hyponatremia as well as urinary sodium losses may reduce serum sodium to 120–125 mEq/L, which protects to some extent against extreme hyperosmolality. However, as dehydration progresses, serum sodium can exceed 140 mEq/L, producing serum osmolality readings of 330–440 mOsm/kg. Ketosis and acidosis are usually absent or mild. Prerenal azotemia

HYPERGLYCEMIC HYPEROSMOLAR STATE



ESSENTIALS OF DIAGNOSIS

- Hyperglycemia > 600 mg/dL (33.3 mmol/L).
- Serum osmolality > 310 mOsm/kg.
- No acidosis; blood pH > 7.3.
- Serum bicarbonate > 15 mEq/L.
- Normal anion gap (< 14 mEq/L).

► General Considerations

This second most common form of hyperglycemic coma is characterized by severe hyperglycemia in the absence of significant ketosis, with hyperosmolality and dehydration. It occurs in patients with mild or occult diabetes, and most

is the rule, with serum urea nitrogen elevations over 100 mg/dL (35.7 mmol/L) being typical.

Treatment

A. Fluid Replacement

Fluid replacement is of paramount importance in treating the nonketotic hyperglycemic state. Fluid deficit may be as much as 6–10 L.

If hypovolemia is present as evidenced by hypotension and oliguria, fluid therapy should be initiated with 0.9% saline. In all other cases, 0.45% saline appears to be preferable as the initial replacement solution because the body fluids of these patients are markedly hyperosmolar. As much as 4–6 L of fluid may be required in the first 8–10 hours. Careful monitoring of the patient is required for proper sodium and water replacement. An important end point of fluid therapy is to restore urinary output to 50 mL/h or more. Once blood glucose reaches 250 mg/dL (13.9 mmol/L), fluid replacement should include 5% dextrose in either water, 0.45% saline solution, or 0.9% saline solution. The rate of dextrose infusion should be adjusted to maintain glycemic levels of 250–300 mg/dL (13.9–16.7 mmol/L) in order to reduce the risk of cerebral edema.

B. Insulin

Less insulin may be required to reduce the hyperglycemia in nonketotic patients as compared to those with diabetic ketoacidotic coma. In fact, fluid replacement alone can reduce hyperglycemia considerably by correcting the hypovolemia, which then increases both glomerular filtration and renal excretion of glucose. Insulin treatment should therefore be delayed unless the patient has significant ketonemia (beta-hydroxybutyrate more than 1 mmol/L). Start the insulin infusion rate at 0.05 unit/kg/h (bolus is not needed) and titrate to lower blood glucose levels by 50–70 mg/dL per hour (2.8–3.9 mmol/L/h). Once the patient has stabilized and the blood glucose falls to around 250 mg/dL (13.9 mmol/L), insulin can be given subcutaneously.

C. Potassium

With the absence of acidosis, there may be no initial hyperkalemia unless associated end-stage chronic kidney disease is present. This results in less severe total potassium depletion than in DKA, and less potassium replacement is therefore needed. However, because initial serum potassium is usually not elevated and because it declines rapidly as a result of insulin's effect on driving potassium intracellularly, it is recommended that potassium replacement be initiated earlier than in ketotic patients, assuming that no chronic kidney disease or oliguria is present. Potassium chloride (10 mEq/L) can be added to the initial bottle of fluids administered if the patient's serum potassium is not elevated.

D. Phosphate

If severe hypophosphatemia (serum phosphate less than 1 mg/dL [0.32 mmol/L]) develops during insulin therapy, phosphate replacement can be given as described for ketoacidotic patients (at 3 mmol/h).

Complications & Prognosis

The severe dehydration and low output state may predispose the patient to complications such as myocardial infarction, stroke, pulmonary embolism, mesenteric vein thrombosis, and disseminated intravascular coagulation. Fluid replacement remains the primary approach to the prevention of these complications. Low-dose heparin prophylaxis is reasonable but benefits of routine anticoagulation remain doubtful. Rhabdomyolysis is a recognized complication and should be looked for and treated.

The overall mortality rate of hyperglycemic hyperosmolar state coma is more than ten times that of DKA, chiefly because of its higher incidence in older patients, who may have compromised cardiovascular systems or associated major illnesses and whose dehydration is often excessive because of delays in recognition and treatment. (When patients are matched for age, the prognoses of these two hyperglycemic emergencies are reasonably comparable.) When prompt therapy is instituted, the mortality rate can be reduced from nearly 50% to that related to the severity of coexistent disorders.

After the patient is stabilized, the appropriate form of long-term management of the diabetes must be determined. Insulin treatment should be continued for a few weeks but patients usually recover sufficient endogenous insulin secretion to make a trial of diet or diet plus oral agents worthwhile. When the episode occurs in a patient who has known diabetes, then education of the patient and caregivers should be instituted. They should be taught how to recognize situations (nausea and vomiting, infection) that predispose to recurrence of the hyperglycemic, hyperosmolar state, as well as detailed information on how to prevent the escalating dehydration that culminates in hyperosmolar coma (small sips of sugar-free liquids, increase in usual hypoglycemic therapy, or early contact with the clinician).

Fayman M et al. Management of hyperglycemic crises: diabetic ketoacidosis and hyperglycemic hyperosmolar state. *Med Clin North Am*. 2017;101:587. [PMID: 28372715]

Scott AR; Joint British Diabetes Societies (JBDS) for Inpatient Care; JBDS hyperosmolar hyperglycaemic guidelines group. Management of hyperosmolar hyperglycaemic state in adults with diabetes. *Diabet Med*. 2015;32:714. [PMID: 25980647]

LACTIC ACIDOSIS



ESSENTIALS OF DIAGNOSIS

- Severe metabolic acidosis with compensatory hyperventilation.
- Blood pH < 7.30.
- Serum bicarbonate < 15 mEq/L.
- Anion gap > 15 mEq/L.
- Absent serum ketones.
- Serum lactate > 5 mmol/L.

► General Considerations

Lactic acidosis is characterized by accumulation of excess lactic acid in the blood. Normally, the principal sources of this acid are the erythrocytes (which lack enzymes for aerobic oxidation), skeletal muscle, skin, and brain. Conversion of lactic acid to glucose and its oxidation principally by the liver but also by the kidneys represent the chief pathways for its removal. Hyperlactatemia and acidosis occur when lactate production exceeds lactate consumption. Causes include tissue hypoxia (global or local), disorders that increase epinephrine levels (severe asthma with excess beta-adrenergic agonist use, cardiogenic or hemorrhagic shock, pheochromocytoma), and drugs that impair oxidative phosphorylation (antiretroviral agents and propofol). Most cases of metformin-associated lactic acidosis occur in patients in whom there were contraindications to the use of metformin, in particular kidney failure. Metformin levels are usually greater than 5 mcg/L when metformin is implicated as the cause of lactic acidosis. Other causes of lactic acidosis include several inborn errors of metabolism and the MELAS syndrome (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes). D-lactic acidosis can occur in patients with short bowel syndrome when unabsorbed carbohydrates are presented as substrate for fermentation by colonic bacteria.

► Clinical Findings

A. Symptoms and Signs

The main clinical feature of lactic acidosis is marked hyperventilation. When lactic acidosis is secondary to tissue hypoxia or vascular collapse, the clinical presentation is variable, being that of the prevailing catastrophic illness. However, in the idiopathic, or spontaneous, variety, the onset is rapid (usually over a few hours), blood pressure is normal, peripheral circulation is good, and there is no cyanosis.

B. Laboratory Findings

Plasma bicarbonate and blood pH are quite low, indicating the presence of severe metabolic acidosis. Ketones are usually absent from plasma and urine or at least not prominent. The first clue may be a high anion gap (serum sodium minus the sum of chloride and bicarbonate anions [in mEq/L] should be no greater than 15). A higher value indicates the existence of an abnormal compartment of anions. If this cannot be clinically explained by an excess of keto acids (diabetes), inorganic acids (uremia), or anions from medication overdosage (salicylates, methyl alcohol, ethylene glycol), then lactic acidosis is probably the correct diagnosis. (See also Chapter 21.) In the absence of azotemia, hyperphosphatemia may be a clue to the presence of lactic acidosis for reasons that are not clear. The diagnosis is confirmed by a plasma lactic acid concentration of 5 mmol/L or higher (values as high as 30 mmol/L have been reported). Normal plasma values average 1 mmol/L, with a normal lactate/pyruvate

ratio of 10:1. This ratio is greatly exceeded in lactic acidosis.¹

► Treatment

Aggressive treatment of the precipitating cause of lactic acidosis is the main component of therapy, such as ensuring adequate oxygenation and vascular perfusion of tissues. Empiric antibiotic coverage for sepsis should be given after culture samples are obtained in any patient in whom the cause of the lactic acidosis is not apparent (Table 30–5).

Alkalization with intravenous sodium bicarbonate to keep the pH above 7.2 has been recommended by some in the emergency treatment of lactic acidosis; as much as 2000 mEq in 24 hours has been used. However, there is no evidence that the mortality rate is favorably affected by administering bicarbonate, and its use remains controversial. Hemodialysis may be useful in cases where large sodium loads are poorly tolerated and in cases associated with metformin toxicity.

► Prognosis

The mortality rate of spontaneous lactic acidosis is high. The prognosis in most cases is that of the primary disorder that produced the lactic acidosis.

DeFronzo R et al. Metformin-associated lactic acidosis: current perspectives on causes and risk. *Metabolism*. 2016;65:20. [PMID: 26773926]

THE HYPOGLYCEMIC STATES

Spontaneous hypoglycemia in adults is of two principal types: fasting and postprandial. Symptoms begin at plasma glucose levels in the range of 60 mg/dL (3.3 mmol/L) and impairment of brain function at approximately 50 mg/dL (2.8 mmol/L). Fasting hypoglycemia is often subacute or chronic and usually presents with neuroglycopenia as its principal manifestation; postprandial hypoglycemia is relatively acute and is often heralded by symptoms of neurogenic autonomic discharge (sweating, palpitations, anxiety, tremulousness).

► Differential Diagnosis (Table 27–11)

Fasting hypoglycemia may occur in certain endocrine disorders, such as hypopituitarism, Addison disease, or myxedema; in disorders related to liver malfunction, such as acute alcoholism or liver failure; and in instances of end-stage chronic kidney disease, particularly in patients requiring dialysis. These conditions are usually obvious, with hypoglycemia being only a secondary feature. When fasting hypoglycemia is a primary manifestation developing in adults without apparent endocrine disorders or inborn metabolic diseases from childhood, the principal

¹In collecting samples, it is essential to rapidly chill and separate the blood in order to remove red cells, whose continued glycolysis at room temperature is a common source of error in reports of high plasma lactate. Frozen plasma remains stable for subsequent assay.

Table 27–11. Common causes of hypoglycemia in adults.¹

Fasting hypoglycemia
Pancreatic B cell tumor
Surreptitious administration of insulin or sulfonylureas
Extrapancreatic tumors
Postprandial hypoglycemia
Gastric surgery
Occult diabetes mellitus
Alcohol-related hypoglycemia
Idiopathic anti-insulin antibodies (which release their bound insulin)
Antibodies to insulin receptors (which act as agonists)
Drug-induced hypoglycemia

¹In the absence of clinically obvious endocrine, kidney, or liver disorders and exclusive of diabetes mellitus treated with hypoglycemic agents.

diagnostic possibilities include (1) hyperinsulinism, due to either pancreatic B cell tumors, iatrogenic or surreptitious administration of insulin or sulfonylurea; and (2) hypoglycemia due to extrapancreatic tumors.

Postprandial (reactive) hypoglycemia may occur after gastrointestinal surgery and is particularly associated with the dumping syndrome after gastrectomy and Roux-en-Y gastric bypass surgery. Occult diabetes very occasionally presents with postprandial hypoglycemia. Rarely, it occurs with islet cell hyperplasia—the so-called noninsulinoma pancreatogenous hypoglycemia syndrome.

Alcohol-related hypoglycemia is due to hepatic glycogen depletion combined with alcohol-mediated inhibition of gluconeogenesis. It is most common in malnourished individuals with excessive alcohol intake but can occur in anyone who is unable to ingest food after an acute alcoholic episode followed by gastritis and vomiting.

Immunopathologic hypoglycemia is an extremely rare condition in which anti-insulin antibodies or antibodies to insulin receptors develop spontaneously.

HYPOGLYCEMIA DUE TO PANCREATIC B CELL TUMORS



ESSENTIALS OF DIAGNOSIS

- ▶ Hypoglycemic symptoms—often neuroglycopenic (confusion, blurred vision, anxiety, convulsions).
- ▶ Immediate recovery upon administration of glucose.
- ▶ Blood glucose < 45 mg/dL (2.5 mmol/L) with a serum insulin level of ≥ 6 microunits/mL.

► General Considerations

Fasting hypoglycemia in an otherwise healthy, well-nourished adult is rare and is most commonly due to an

adenoma of the islets of Langerhans. Ninety percent of such tumors are single and benign, but multiple adenomas can occur as well as malignant tumors with functional metastases. Adenomas may be familial, and multiple adenomas have been found in conjunction with tumors of the parathyroids and pituitary (MEN type 1 [MEN 1]). About 30% of sporadic insulinoma tumors have a somatic mutation in the YY1 gene (T372R) that encodes the transcriptional repressor YY1. Over 99% of insulinomas are located within the pancreas and less than 1% in ectopic pancreatic tissue.

► Clinical Findings

A. Symptoms and Signs

The most important prerequisite to diagnosing an insulinoma is simply to consider it, particularly in relatively healthy-appearing persons who have fasting hypoglycemia associated with some degree of central nervous system dysfunction such as confusion or abnormal behavior. A delay in diagnosis can result in unnecessary treatment for psychomotor epilepsy or psychiatric disorders and may cause irreversible brain damage. In long-standing cases, obesity can result as a consequence of overeating to relieve symptoms.

The so-called Whipple triad is characteristic of hypoglycemia regardless of the cause. It consists of (1) a history of hypoglycemic symptoms, (2) an associated low plasma glucose level (40–50 mg/dL), and (3) relief of symptoms upon ingesting fast-acting carbohydrates in approximately 15 minutes. The hypoglycemic symptoms in insulinoma often develop in the early morning or after missing a meal. Occasionally, they occur after exercise.

Patients typically complain of neuroglycopenic symptoms such as blurred vision or diplopia, headache, feelings of detachment, slurred speech, and weakness. Personality and mental changes vary from anxiety to psychotic behavior, and neurologic deterioration can result in convulsions or coma. Hypoglycemic unawareness is very common and adrenergic symptoms of palpitations and sweating may be blunted. With the ready availability of home blood glucose-monitoring systems, patients sometimes present with documented fingerstick blood glucose levels in 40s and 50s at time of symptoms. Access to sulfonylureas or insulin should be explored—does a family member have diabetes, or does the patient or family member work in the medical field? Medication-dispensing errors should be excluded—has the patient's prescription medication changed in shape or color? Patients with insulinoma or factitious hypoglycemia usually have a normal physical examination.

B. Laboratory Findings

B cell adenomas do not reduce secretion of insulin in the presence of hypoglycemia, and the critical diagnostic test is to demonstrate inappropriately elevated serum insulin, proinsulin, and C-peptide levels, at a time when plasma glucose level is below 45 mg/dL.

The diagnostic criteria for insulinoma after a 72-hour fast are listed in Table 27–12. Other causes of hyperinsulinemic hypoglycemia include factitious administration of

Table 27–12. Diagnostic criteria for insulinoma after a 72-hour fast.

Laboratory Test	Result
Plasma glucose	< 45 mg/dL (2.5 mmol/L)
Plasma insulin (RIA)	≥ 6 microunits/mL (36 pmol/L)
Plasma insulin (ICMA)	≥ 3 microunits/mL (18 pmol/L)
Plasma C-peptide	≥ 200 pmol/L (0.2 nmol/L, 0.6 ng/mL)
Plasma proinsulin	≥ 5 pmol/L
Beta-hydroxybutyrate	≤ 2.7 mmol/L
Sulfonylurea screen (including repaglinide and nateglinide)	Negative

ICMA, immunochemiluminometric assays; RIA, radioimmunoassay.

insulin or sulfonylureas. Factitious use of insulin will result in suppression of endogenous insulin secretion and low C-peptide levels. In patients who have injected insulin, the insulin/C-peptide ratio (pmol/L) will be greater than 1. An elevated circulating proinsulin level in the presence of fasting hypoglycemia is characteristic of most B cell adenomas and does not occur in factitious hyperinsulinism. Thus, C-peptide levels (by immunochemiluminometric assays [ICMA]) of greater than 200 pmol/L and proinsulin levels (by radioimmunoassay [RIA]) of greater than 5 pmol/L are characteristic of insulinomas. In patients with insulinoma, plasma beta-hydroxybutyrate levels are suppressed to 2.7 mmol/L or less. No single hormone measurement (insulin, proinsulin, C-peptide) is 100% sensitive and specific for the diagnosis of insulinoma, and insulinoma cases have been reported with insulin levels below 3 microunits/mL (ICMA assay) or proinsulin level below 5 pmol/L. These hormonal assays are also not standardized, and there can be significant variation in the test results. Therefore, the diagnosis should be based on multiple biochemical parameters.

In patients with epigastric distress, a history of renal calculi, or menstrual or erectile dysfunction, a serum calcium, gastrin, or prolactin level may be useful in screening for MEN 1 associated with insulinoma.

C. Diagnostic Tests

If the history is consistent with episodic spontaneous hypoglycemia, patients should be given a home blood glucose monitor and advised to monitor blood glucose levels at the time of symptoms and before consumption of carbohydrates, if this can be done safely. Patients with insulinomas frequently report fingerstick blood glucose levels between 40 mg/dL (2.2 mmol/L) and 50 mg/dL (2.8 mmol/L) at the time of symptoms. The diagnosis, however, cannot be made based on a fingerstick blood glucose. It is necessary to have a low laboratory glucose concomitantly with elevated plasma insulin, proinsulin, and C-peptide levels and a negative sulfonylurea screen. When patients give a history of symptoms after only a short period of food withdrawal or with exercise, then an outpatient assessment can

be attempted. The patient should be brought by a family member to the office after an overnight fast and observed in the office. Activity such as walking should be encouraged and fingerstick blood glucose measured repeatedly during observation. If symptoms occur or fingerstick blood glucose is below 50 mg/dL (2.8 mmol/L), then samples for plasma glucose, insulin, C-peptide, proinsulin, sulfonylurea screen, serum ketones, and antibodies to insulin should be sent. If outpatient observation does not result in symptoms or hypoglycemia and if the clinical suspicion remains high, then the patient should undergo an inpatient supervised 72-hour fast. A suggested protocol for the supervised fast is shown in Table 27–13.

In 30% of patients with insulinoma, the blood glucose levels often drop below 45 mg/dL (2.5 mmol/L) after an overnight fast, but some patients require up to 72 hours to develop symptomatic hypoglycemia. However, the term “72-hour fast” is actually a misnomer in most cases since the fast should be immediately terminated as soon as symptoms appear and laboratory confirmation of hypoglycemia is available. In normal male subjects, the blood glucose does not fall below 55–60 mg/dL (3.1–3.3 mmol/L) during a 3-day fast. In contrast, in normal premenopausal women, the plasma glucose can reach values as low as 35 mg/dL (1.9 mmol/L). In these cases, however, the women are not symptomatic, presumably owing to the development of sufficient ketonemia to supply energy needs to the brain. Insulinoma patients, on the other hand,

Table 27–13. Suggested hospital protocol for supervised fast in diagnosis of insulinoma.

- (1) Place intravenous cannula and obtain baseline plasma glucose, insulin, proinsulin, beta-hydroxybutyrate, and C-peptide measurements at onset of fast.
- (2) Permit only calorie-free and caffeine-free fluids and encourage supervised activity (such as walking).
- (3) Obtain fingerstick glucose measurements every 4 hours until values < 60 mg/dL are obtained. Then increase the frequency of fingersticks to 1–2 hours, and when capillary glucose value is < 45 mg/dL send a venous blood sample to the laboratory for plasma glucose.¹ Check frequently for manifestations of neuroglycopenia.
- (4) At 48 hours into the fast, send a venous blood sample for plasma glucose, insulin, proinsulin, C-peptide, beta-hydroxybutyrate, and sulfonylurea measurement.
- (5) If symptoms of hypoglycemia occur or if a laboratory value of serum glucose is < 45 mg/dL, or if 72 hours have elapsed, conclude the fast with a final blood sample for plasma glucose,¹ insulin, proinsulin, C-peptide, beta-hydroxybutyrate, and sulfonylurea measurements. Then give oral fast-acting carbohydrate followed by a meal. If the patient is confused or unable to take oral agents, administer 50 mL of 50% dextrose intravenously over 3–5 minutes. Do not conclude a fast based simply on a capillary blood glucose measurement—wait for the laboratory glucose value—unless the patient is very symptomatic and it would be dangerous to wait.

¹Glucose sample should be collected in sodium fluoride containing tube on ice to prevent glycolysis and the plasma separated immediately upon receipt at the laboratory. Arrange for the laboratory to run the glucose samples “stat.”

become symptomatic when plasma glucose drops to subnormal levels, since inappropriate insulin secretion restricts ketone formation. Moreover, the demonstration of a non-suppressed insulin level of 3 microunits/mL or more using an ICMA assay (greater than 6 microunits/mL using an RIA assay) in the presence of hypoglycemia suggests the diagnosis of insulinoma. If hypoglycemia does not develop in a male patient after fasting for up to 72 hours—and particularly when this prolonged fast is terminated with a period of moderate exercise—insulinoma must be considered an unlikely diagnosis.

An oral glucose tolerance test is of no value in the diagnosis of insulin-secreting tumors. HbA_{1c} levels may be low but there is considerable overlap with normal patients and no particular value is diagnostic.

D. Preoperative Localization of B Cell Tumors

After the diagnosis of insulinoma has been unequivocally made by clinical and laboratory findings, studies to localize the tumor should be initiated. Most tumors are in the pancreas, and ectopic cases are rare.

Because of the small size of these tumors (averaging 1.5 cm in diameter in one large series), imaging studies do not necessarily identify all of them. A pancreatic dual phase helical CT scan with thin section can identify 82–94% of the lesions. MRI scans with gadolinium can be helpful in detecting a tumor in 85% of cases. One case report suggests that diffusion-weighted MRI can be useful for detecting and localizing small insulinomas, especially for those with no hypervascular pattern. PET/CT scans using gallium-labeled somatostatin analogs such as DOTA-1-NaI₃-octreotide (DOTA-NOC), which have a higher affinity for somatostatin receptor subtypes 2, 3, and 5, have been reported to be useful in localizing the tumors. Insulinomas express GLP-1 receptors, and radiolabeled GLP-1 receptor agonists such as Lys(40)(Ahx-hydrazinonicotinamide [HYNIC]-[(99m)Tc]NH(2)]-exendin-4 for SPECT/CT have also been reported to visualize the tumors. If the imaging study is normal, then an endoscopic ultrasound should be performed. In experienced hands, about 80–90% of tumors can be detected with this procedure. Fine-needle aspiration of the identified lesion can be attempted to confirm the presence of a neuroendocrine tumor. If the tumor is not identified or the imaging result is equivocal, then the patient should undergo selective calcium-stimulated angiography, which has been reported to localize the tumor to a particular region of the pancreas approximately 90% of the time. In this test, angiography is combined with injections of calcium gluconate into the gastroduodenal, splenic, and superior mesenteric arteries, and insulin levels are measured in the hepatic vein effluent. The procedure is performed after an overnight fast. Calcium stimulates insulin release from insulinomas but not normal islets, and so a step-up from baseline in insulin levels (twofold or greater) regionalizes the source of the hyperinsulinism to the head of the pancreas for the gastroduodenal artery, the uncinate process for the superior mesenteric artery, and the body and tail of the pancreas for the splenic artery calcium infusions. These studies combined with careful intraoperative ultrasonography and palpation by a surgeon

experienced in insulinoma surgery identifies up to 98% of tumors.

Treatment

The treatment of choice for insulin-secreting tumors is surgical resection. While waiting for surgery, patients should be given oral diazoxide. Divided doses of 300–400 mg/day usually suffice, although an occasional patient may require up to 800 mg/day. Side effects include edema due to sodium retention, gastric irritation, and mild hirsutism. Hydrochlorothiazide, 25–50 mg daily, can be used to counteract the sodium retention and edema as well potentiate diazoxide's hyperglycemic effect.

In patients with a single benign pancreatic B cell adenoma, 90–95% have a successful cure at the first surgical attempt when intraoperative ultrasound is used by a skilled surgeon. Diazoxide should be administered on the day of the surgery because it reduces the risk of hypoglycemia during surgery. Typically, it does not mask the glycemic rise indicative of surgical cure. Blood glucose should be monitored throughout surgery, and 5% or 10% dextrose infusion should be used to maintain euglycemia. In cases where the diagnosis has been established but no adenoma is located after careful palpation and use of intraoperative ultrasound, it is no longer advisable to blindly resect the body and tail of the pancreas, since a nonpalpable tumor missed by ultrasound is most likely embedded within the fleshy head of the pancreas that is left behind with subtotal resections. Most surgeons prefer to close the incision and schedule a selective arterial calcium stimulation with hepatic venous sampling to locate the tumor site prior to a repeat operation. Laparoscopy using ultrasound and enucleation has been successful with a single tumor of the body or tail of the pancreas, but open surgery remains necessary for tumors in the head of the pancreas.

In patients with inoperable functioning islet cell carcinoma with and without hepatic metastasis and in approximately 5–10% of MEN 1 cases when subtotal removal of the pancreas has failed to produce cure, the treatment approach is the same as for other types of pancreatic neuroendocrine tumors (pNETs). Diazoxide is the treatment of choice in preventing hypoglycemia. Frequent carbohydrate feedings (every 2–3 hours) can also be helpful, although weight gain can become a problem. Somatostatin analogs, octreotide or lanreotide, should be considered if diazoxide is ineffective or if there is tumor progression. Surgery or embolization (bland, chemo- and radio-) or thermal ablation (radiofrequency, microwave, and cryoablation) can be used to reduce tumor burden and also provide symptomatic relief. Chemotherapy regimens that can be considered include combination of streptozocin, 5-fluorouracil, and doxorubicin; capecitabine and oxaliplatin; and capecitabine and temozolomide (Table 39–3). Targeted therapies against multiple steps in the PI3K/AKT/mTor pathway have been shown to be helpful. Everolimus, an inhibitor of mTor, is approved for treatment of advanced pNETs. Sunitinib has been shown to slow growth of pNETs. Treatment with radioisotopes (indium-111 or yttrium-90 or lutetium-177) linked to a somatostatin analog has been reported to show benefit in a proportion of patients.

NONISLET CELL TUMOR HYPOGLYCEMIA

These rare causes of hypoglycemia include mesenchymal tumors such as retroperitoneal sarcomas, hepatocellular carcinomas, adrenocortical carcinomas, and miscellaneous epithelial-type tumors. The tumors are frequently large and readily palpated or visualized on CT scans or MRI.

In many cases the hypoglycemia is due to the expression and release of an incompletely processed insulin-like growth factor 2 (IGF-2) by the tumor.

The diagnosis is supported by laboratory documentation of serum insulin levels below 5 microunit/mL with plasma glucose levels of 45 mg/dL (2.5 mmol/L) or lower. Values for growth hormone and IGF-1 are also decreased. Levels of IGF-2 may be increased but often are “normal” in quantity, despite the presence of the immature, higher-molecular-weight form of IGF-2, which can be detected only by special laboratory techniques.

Not all the patients with nonislet cell tumor hypoglycemia have elevated pro-IGF-2. Ectopic insulin production has been described in bronchial carcinoma, ovarian carcinoma, and small cell carcinoma of the cervix. Hypoglycemia due to IgF-1 released from a metastatic large cell carcinoma of the lung has also been reported. GLP-1-secreting tumors (ovarian and pNETs) can also cause hypoglycemia by stimulating insulin release from normal pancreatic islets.

The prognosis for these tumors is generally poor, and surgical removal should be attempted when feasible. Dietary management of the hypoglycemia is the mainstay of medical treatment, since diazoxide is usually ineffective.

POSTPRANDIAL HYPOGLYCEMIA

1. Hypoglycemia Following Gastric Surgery

Hypoglycemia sometimes develops in patients who have undergone gastric surgery (eg, gastrectomy, vagotomy, pyloroplasty, gastrojejunostomy, Nissan fundoplication, Billroth II procedure, and Roux-en-Y), especially when they consume foods containing high levels of readily absorbable carbohydrates. This late dumping syndrome occurs about 1–3 hours after a meal and is a result of rapid delivery of high concentration of carbohydrates in the proximal small bowel and rapid absorption of glucose. The hyperinsulinemic response to the high carbohydrate load causes hypoglycemia. Excessive release of gastrointestinal hormones such as GLP-1 likely play a role in the hyperinsulinemic response. The symptoms include lightheadedness, sweating, confusion and even loss of consciousness after eating a high carbohydrate meal. To document hypoglycemia, the patient should consume a meal that leads to symptoms during everyday life. An oral glucose tolerance test is not recommended because many normal persons have false-positive test results. There have been case reports of insulinoma and noninsulinoma pancreatogenous hypoglycemia syndrome in patients with hypoglycemia post Roux-en-Y surgery. It is unclear how often this occurs. A careful history may identify patients who have a history of hypoglycemia with exercise or missed meals, and these individuals may require a formal 72-hour fast to rule out an insulinoma.

Treatment for secondary dumping includes dietary modification, but this may be difficult to sustain. Patients can try more frequent meals with smaller portions of less rapidly digested carbohydrates. Alpha-glucosidase therapy may be a useful adjunct to a low carbohydrate diet. Octreotide 50 mcg administered subcutaneously two or three times a day 30 minutes prior to each meal has been reported to improve symptoms due to late dumping syndrome. Treatment with exendin 9-39, a GLP-1 receptor agonist, may prevent post gastric bypass hypoglycemia. SGLT2 inhibitors may ameliorate the postprandial glucose rise, the subsequent insulin response, and hypoglycemia. There is a report of a patient with Roux-en-Y surgery who had complete resolution of both hyperglycemia and hypoglycemia when she was given canagliflozin. Various surgical procedures to delay gastric emptying have been reported to improve symptoms but long-term efficacy studies are lacking.

2. Functional Alimentary Hypoglycemia

Patients have symptoms suggestive of increased sympathetic activity, including anxiety, weakness, tremor, sweating or palpitations after meals. Physical examination and laboratory tests are normal. It is not recommended that patients with symptoms suggestive of increased sympathetic activity undergo either a prolonged oral glucose tolerance test or a mixed meal test. Instead, the patients should be given home blood glucose monitors (with memories) and instructed to monitor fingerstick glucose levels at the time of symptoms. Only patients who have symptoms when their fingerstick blood glucose is low (less than 50 mg/dL) and who have resolution of symptoms when the glucose is raised by eating rapidly released carbohydrate need additional evaluation. Patients who do not have evidence for low glucose levels at time of symptoms are generally reassured by their findings. Counseling and support should be the mainstays in therapy, with dietary manipulation only an adjunct.

3. Occult Diabetes

This condition is characterized by a delay in early insulin release from pancreatic B cells, resulting in initial exaggeration of hyperglycemia during a glucose tolerance test. In response to this hyperglycemia, an exaggerated insulin release produces a late hypoglycemia 4–5 hours after ingestion of glucose. These patients are often obese and frequently have a family history of diabetes mellitus.

Patients with this type of postprandial hypoglycemia often respond to reduced intake of refined sugars with multiple, spaced, small feedings high in dietary fiber. In the obese, treatment is directed at weight reduction to achieve ideal weight. These patients should be considered to have prediabetes or early diabetes (type 1 or 2) and advised to have periodic medical evaluations.

4. Autoimmune Hypoglycemia

Patients with autoimmune hypoglycemia have early postprandial hyperglycemia followed by hypoglycemia 3–4 hours later. The hypoglycemia is attributed to a dissociation of insulin antibody immune complexes, releasing free insulin.

The disorder is associated with methimazole treatment for Graves disease, although it can also occur in patients treated with various other sulphydryl-containing medications (captopril, penicillamine) as well as other drugs such as hydralazine, isoniazid, and procainamide. In addition, it has been reported in patients with autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus, and polymyositis as well as in plasma cell myeloma and other plasma cell dyscrasias where paraproteins or antibodies cross-react with insulin. There is also an association with the HLA class II alleles (DRB1*0406, DQA1*0301, and DQB1*0302). These alleles are 10 to 20 times more common in Japanese and Korean populations, which explains why the disorder has been reported mostly in Japanese patients.

High titers of insulin autoantibodies, usually IgG class, can be detected. Insulin, proinsulin, and C-peptide levels may be elevated, but the results may be erroneous because of the interference of the insulin antibodies with the immunoassays for these peptides.

In most cases, the hypoglycemia is transient and usually resolves spontaneously within 3–6 months of diagnosis, particularly when the offending medications are stopped. The most consistent therapeutic benefit in management of this syndrome has been achieved by dietary treatment with small, frequent low-carbohydrate meals. Prednisone (30–60 mg orally daily) has been used to lower the titer of insulin antibodies.

FACTITIOUS HYPOGLYCEMIA

Factitious hypoglycemia may be difficult to document. A suspicion of self-induced hypoglycemia is supported when the patient is associated with the health professions or has access to diabetic medications taken by a diabetic member of the family. The triad of hypoglycemia, high immunoreactive insulin, and suppressed plasma C-peptide immunoreactivity is pathognomonic of exogenous insulin administration. Insulin and C-peptide are secreted in a 1:1 molar ratio. A large fraction of the endogenous insulin is cleared by the liver, whereas C-peptide, which is cleared by the kidney, has a lower metabolic clearance rate. For this reason, the molar ratio of insulin and C-peptide in a hypoglycemic patient should be less than 1.0 in cases of insulinoma and is greater than 1.0 in cases of exogenous insulin administration (see Hypoglycemia Due to Pancreatic B Cell Tumors, above). When sulfonylureas, repaglinide, and nateglinide are suspected as a cause of factitious hypoglycemia, a plasma level of these medications to detect their presence may be required to distinguish laboratory findings from those of insulinoma.

HYPOGLYCEMIA DUE TO INSULIN RECEPTOR ANTIBODIES

Hypoglycemia due to insulin receptor autoantibodies is an extremely rare syndrome; most cases have occurred in women often with a history of autoimmune disease. Almost all of these patients have also had episodes of insulin-resistant diabetes and acanthosis nigricans. Their hypoglycemia may be either fasting or postprandial and is often severe

and is attributed to an agonistic action of the antibody on the insulin receptor. Balance between the antagonistic and agonistic effects of the antibodies determines whether insulin-resistant diabetes or hypoglycemia occurs. Hypoglycemia was found to respond to corticosteroid therapy but not to plasmapheresis or immunosuppression.

MEDICATION- & ETHANOL-INDUCED HYPOGLYCEMIA

A number of medications apart from diabetic medications can occasionally cause hypoglycemia. Common offenders include the fluoroquinolones such as gatifloxacin and levofloxacin, pentamidine, quinine, ACE inhibitors, salicylates and beta-adrenergic blocking agents. The fluoroquinolones, particularly gatifloxacin, have been associated with both hypoglycemia and hyperglycemia. It is thought that the drug acts on the ATP sensitive potassium channels in the beta cell. Hypoglycemia is an early event, and hyperglycemia occurs several days into therapy. Intravenous pentamidine is cytotoxic to beta cells and causes acute hyperinsulinemia and hypoglycemia followed by insulinopenia and hyperglycemia. Fasting patients taking noncardioselective beta-blockers can have an exaggerated hypoglycemic response to starvation. The beta-blockade inhibits fatty acids and gluconeogenesis substrate release and reduces plasma glucagon response. Therapy with ACE inhibitors increases the risk of hypoglycemia in patients who are taking insulin or sulfonylureas presumably because these drugs increase sensitivity to circulating insulin by increasing blood flow to the muscle. Some opioids cause hypoglycemia. Tramadol use has been associated with increased risk of hospitalization for hypoglycemia. Methadone overdose has also been reported to cause hypoglycemia and a rapid dose escalation of methadone in cancer patients can lower glucose levels.

Ethanol-associated hypoglycemia may be due to hepatic alcohol dehydrogenase activity depleting NAD. The resultant change in the redox state—increase in NADH to NAD⁺ ratio—causes a partial block at several points in the gluconeogenic pathway. With prolonged starvation, glycogen reserves become depleted within 18–24 hours and hepatic glucose output becomes totally dependent on gluconeogenesis. Under these circumstances, a blood concentration of ethanol as low as 45 mg/dL (9.8 mmol/L) can induce profound hypoglycemia by blocking gluconeogenesis. Neuroglycopenia in a patient whose breath smells of alcohol may be mistaken for alcoholic stupor. Prevention consists of adequate food intake during ethanol ingestion. Therapy consists of glucose administration to replenish glycogen stores until gluconeogenesis resumes.

When sugar-containing soft drinks are used as mixers to dilute alcohol in beverages (gin and tonic, rum and cola), there seems to be a greater insulin release than when the soft drink alone is ingested and a tendency for more of a late hypoglycemic overshwing to occur 3–4 hours later. Prevention would consist of avoiding sugar mixers while ingesting alcohol and ensuring supplementary food intake to provide sustained absorption.

28

Lipid Disorders

Michael J. Blaha, MD, MPH

The “Lipid Hypothesis” of cardiovascular disease (CVD)—stating that cholesterol is causal in the development of atherosclerotic cardiovascular disease (ASCVD) and that lowering of cholesterol is associated with lower cardiovascular event rates—is widely accepted throughout the medical community. For patients with known CVD (secondary prevention), studies have shown that cholesterol lowering leads to a consistent reduction in total mortality and in recurrent cardiovascular events in men and women; other studies have documented lowered mortality and events in middle-aged and older patients. Among patients without CVD (primary prevention), the data are generally consistent, with rates of cardiovascular events, heart disease mortality, and all-cause mortality differing among studies. Treatment guidelines have been designed to assist clinicians in selecting patients for cholesterol-lowering therapy based predominantly on their overall risk of developing CVD as well as their baseline cholesterol levels.

There are several genetic disorders that provide insight into the pathogenesis of lipid-related diseases. **Familial hypercholesterolemia**, rare in the homozygous state (about one per million), causes markedly high low-density lipoprotein (LDL) levels and early CVD. The most common genetic defects involve absent or defective LDL receptors, resulting in unregulated LDL metabolism, genetic mutations of apolipoprotein B, or gain of function in proprotein convertase subtilisin/kexin type 9 (PCSK9), a protein that regulates breakdown of LDL receptors. Patients with two abnormal genes (homozygotes) have extremely high levels—up to eight times normal—and present with atherosclerotic disease in childhood. Patients with two abnormal genes (homozygotes) may require liver transplantation or plasmapheresis to correct their severe lipid abnormalities; early treatment with statins appears to confer lifetime benefits in such patients. Those with one defective gene (heterozygotes) have LDL concentrations up to two or three times normal; persons with this condition may develop CVD in their 30s or 40s.

Another rare condition is caused by an abnormality of lipoprotein lipase, the enzyme that enables peripheral tissues to take up triglyceride from chylomicrons and very-low-density lipoprotein (VLDL) particles. Patients with this condition, one cause of **familial chylomicronemia**

syndrome, have marked hypertriglyceridemia with recurrent pancreatitis and hepatosplenomegaly in childhood.

Numerous other genetic abnormalities of lipid metabolism are named for the abnormality noted when serum is electrophoresed (eg, dysbetalipoproteinemia, characterized by elevated levels of remnant lipoproteins) or from polygenic combinations of lipid abnormalities in families (eg, familial combined hyperlipidemia).

► When to Refer

- Known genetic lipid disorders.
- Striking family history of hyperlipidemia or premature atherosclerosis.
- Extremely high serum LDL cholesterol or triglycerides, or extremely low serum high-density lipoprotein (HDL) cholesterol.

Chyzyk V et al. Familial chylomicronemia syndrome: a rare but devastating autosomal recessive disorder characterized by refractory hypertriglyceridemia and recurrent pancreatitis. Trends Cardiovasc Med. 2020;30:80. [PMID: 31003756]

Hegele RA et al. Rare dyslipidaemias, from phenotype to genotype to management: a European Atherosclerosis Society task force consensus statement. Lancet Diabetes Endocrinol. 2020;8:50. [PMID: 31582260]

Khera AV et al. What is familial hypercholesterolemia, and why does it matter? Circulation. 2020;141:1760. [PMID: 32479201]

Mortensen MB et al. Elevated LDL cholesterol and increased risk of myocardial infarction and atherosclerotic cardiovascular disease in individuals aged 70–100 years: a contemporary primary prevention cohort. Lancet. 2020;396:1644. [PMID: 33186534]

Sniderman AD et al. Apolipoprotein B particles and cardiovascular disease: a narrative review. JAMA Cardiol. 2019;4:1287. [PMID: 31642874]

LIPID FRACTIONS & THE RISK OF CORONARY HEART DISEASE

In serum, cholesterol is carried primarily on three different lipoproteins—the VLDL, LDL, and HDL molecules. Total cholesterol equals the sum of these three components:

$$\text{Total cholesterol} = \text{HDL cholesterol} + \text{VLDL cholesterol} + \text{LDL cholesterol}$$

Using these assumptions, the Friedewald equation states that LDL cholesterol can be estimated as:

$$\text{LDL cholesterol} = \frac{\text{Total cholesterol} - \text{HDL cholesterol} - \frac{\text{Triglycerides (mg/dL)}}{5}}{\text{(mg/dL) (mg/dL)}}$$

When using SI units, the formula becomes

$$\text{LDL cholesterol} = \frac{\text{Total cholesterol} - \text{HDL cholesterol} - \frac{\text{Triglycerides (mmol/L)}}{2.2}}{\text{(mmol/L) (mmol/L)}}$$

Modern research has questioned several of the assumptions underlying the Friedewald equation, particularly the assumption that VLDL is always best estimated as triglycerides/5, which is inaccurate when triglycerides are above 150 mg/dL and when LDL cholesterol is less than 70 mg/dL. Therefore, many commercial laboratories have switched to the Martin/Hopkins equation, which uses a flexible factor for deriving VLDL from triglycerides (as opposed to always using 5). The Martin/Hopkins equation reduces the systematic underestimation of LDL cholesterol when triglycerides are greater than 150 mg/dL and LDL is less than 70 mg/dL, and is more accurate in estimating LDL from nonfasting blood specimens.

Non-HDL cholesterol is increasingly recognized as an important measure of the total quantity of apolipoprotein B-containing atherogenic lipid particles. Non-HDL cholesterol is calculated as: total cholesterol – HDL cholesterol. Advantages of calculating non-HDL cholesterol are that it is directly measured, requires no additional cost, is less sensitive to fasting status, and is a better predictor of cardiovascular risk compared to LDL cholesterol.

Lipoprotein(a), a subfraction of LDL that is largely genetically determined, has also been recognized as a causal factor in atherosclerosis. One-time measurement of lipoprotein(a) in patients with a strong family history, with manifestations of early ASCVD, or with familial hypercholesterolemia is useful. The National Lipid Association also recommends cascade screening in family members of those with severe hypercholesterolemia, including elevated lipoprotein(a). Values greater than 50 mg/dL or greater than 100 nmol/L are considered elevated. The 2019 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines recommend one-time lipoprotein(a) measurement for all adults to identify those with very high values (greater than 180 mg/dL or greater than 430 nmol/L). Novel antisense oligonucleotide therapies directed at lipoprotein(a) are currently being tested in phase 3 trials of patients with prior myocardial infarction. Currently, lipoprotein(a) is used as a risk-enhancing factor favoring early statin treatment.

It is difficult to assign a “normal” range for serum lipids. This is because our cholesterol values are vastly higher than our evolutionary ancestors (whose LDL cholesterol may have been 30–50 mg/dL) and because mean values vary across the world. Mean LDL cholesterol levels are currently declining in the United States, including in youths. There is no evidence currently available that adult cholesterol levels

can be “too low”; that is, there is no evidence that very low LDL cholesterol is linked with any side effects (eg, cognitive dysfunction).

Sampson M et al. A new equation for calculation of low-density lipoprotein cholesterol in patients with normolipidemia and/or hypertriglyceridemia. *JAMA Cardiol.* 2020;5:540. [PMID: 32101259]

Sathiyakumar V et al. Fasting versus nonfasting and low-density lipoprotein cholesterol accuracy. *Circulation.* 2018;137:10. [PMID: 29038168]

Wilson DP et al. Use of lipoprotein(a) in clinical practice: a biomarker whose time has come. A scientific statement from the National Lipid Association. *J Clin Lipidol.* 2019;13:374. [PMID: 31147269]

THERAPEUTIC EFFECTS OF LOWERING CHOLESTEROL

Reducing cholesterol levels in healthy middle-aged men without coronary heart disease (CHD) (in **primary prevention studies**) reduces risk in direct proportion to the reduction in LDL cholesterol. Treated adults have clinically important reductions in the rates of myocardial infarctions, new cases of angina, need for coronary artery bypass or other revascularization procedures, peripheral artery disease, and stroke. The West of Scotland Study showed a 31% decrease in myocardial infarctions in middle-aged men treated with pravastatin compared with placebo. The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) study showed similar results with lovastatin. As with any primary prevention interventions, large numbers of healthy patients need to be treated to prevent a single event. The numbers of patients needed to treat (NNT) to prevent one nonfatal myocardial infarction or one coronary artery disease death in these two studies were 46 and 50, respectively. The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) study of atorvastatin in persons with hypertension and other risk factors but without CHD demonstrated a 36% reduction in CHD events. The Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study showed a 44% reduction in a combined end point of myocardial infarction, stroke, revascularization, hospitalization for unstable angina, or death from cardiovascular causes in both men and women. The NNT for 1 year to prevent one event was 169. The Heart Outcomes Prevention Evaluation (HOPE-3) trial of rosuvastatin showed a 24% reduction in cardiovascular events. The NNT over 5.6 years was 91.

Primary prevention studies have found a less consistent effect on total mortality. The West of Scotland study found a 20% decrease in total mortality. The AFCAPS/TexCAPS study with lovastatin showed no difference in total mortality. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT) also showed no reduction either in all-cause mortality or in CHD events when pravastatin was compared with usual care. Persons treated with atorvastatin in the ASCOT study had a 13% reduction in mortality, but the result was not statistically significant. The JUPITER trial demonstrated a statistically

significant 20% reduction in death from any cause. The NNT for 1 year was 400. The HOPE-3 trial showed a 7% reduction in all-cause mortality, but the result was not statistically significant.

In **secondary prevention studies** among patients with established CVD, the mortality benefits of cholesterol lowering are clearer. Major trials with statins have shown significant reductions in cardiovascular events, cardiovascular deaths, and all-cause mortality in men and women with coronary artery disease. The NNT to prevent a nonfatal myocardial infarction or a coronary artery disease death in these studies was between 12 and 34. Aggressive cholesterol lowering with these agents causes regression of atherosclerotic plaques in some patients, reduces the progression of atherosclerosis in saphenous vein grafts, and can slow or reverse carotid artery atherosclerosis. Results with other classes of medications, particularly those with little effect on LDL or the LDL receptor, have been less consistent. The benefits and adverse effects of cholesterol lowering may be specific to each type or mechanism of drug; the clinician cannot assume that the effects of new drugs with novel mechanisms of action will generalize to other classes of medication.

The disparities in absolute event lowering between primary and secondary prevention studies highlight a critical aspect of clinical cholesterol lowering. The net benefits from cholesterol lowering depend on the underlying risk of ASCVD as well as the competing risks of other diseases. In middle-aged patients with atherosclerosis and high cholesterol, morbidity and mortality rates are high, and measures that reduce cholesterol-related risk are more likely to provide a robust net benefit to the patient. In older patients with little atherosclerosis and lower cholesterol levels, there may be no meaningful net benefit to cholesterol lowering.

- Arnett DK et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2019;74:1376. [PMID: 30894319]
- Grundy SM et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary. *Circulation.* 2019;139:e1046. [PMID: 30565953]
- Michos ED et al. Lipid management for the prevention of atherosclerotic cardiovascular disease. *N Engl J Med.* 2019;381:1557. [PMID: 31618541]
- Navarese EP et al. Association between baseline LDL-C level and total and cardiovascular mortality after LDL-C lowering: a systematic review and meta-analysis. *JAMA.* 2018;319:1566. [PMID: 29677301]
- Ray KK et al. Pharmacological lipid-modification therapies for prevention of ischaemic heart disease: current and future options. *Lancet.* 2019;394:697. [PMID: 31448741]

SECONDARY CONDITIONS THAT AFFECT LIPID METABOLISM

Several factors, including drugs, can influence serum lipids. These are important for two reasons: abnormal lipid levels (or changes in lipid levels) may be the presenting sign of some of these conditions, and correction of the

underlying condition may obviate the need to treat an apparent lipid disorder. Thyroid disease, particularly hypothyroidism, is associated with a high LDL. Poorly controlled diabetes mellitus and alcohol use, in particular, are commonly associated with high triglyceride levels that decline with improvements in glycemic control or reduction in alcohol use, respectively. Thus, secondary causes of high blood lipids should be considered in each patient with a lipid disorder before lipid-lowering therapy is started. In most instances, special testing is not needed: a history and physical examination are sufficient.

CLINICAL PRESENTATIONS

Most patients with high cholesterol levels have no specific symptoms or signs. The vast majority of patients with lipid abnormalities are detected by the laboratory, either as part of the workup of a patient with CVD or as part of a preventive screening strategy. Extremely high levels of chylomicrons or VLDL particles (triglyceride level above 1000 mg/dL or 10 mmol/L) result in the formation of **eruptive xanthomas** (Figure 28-1) (red-yellow papules, especially on the buttocks). High LDL concentrations result in **tendinous xanthomas** on certain tendons (Achilles, patella, back of the hand). Such xanthomas usually indicate one of the underlying genetic hyperlipidemias. **Lipemia retinalis** (cream-colored blood vessels in the fundus) is seen with extremely high triglyceride levels (above 2000 mg/dL or 20 mmol/L).

SCREENING & TREATMENT OF HIGH BLOOD CHOLESTEROL

While screening of all children for cholesterol disorders remains controversial, all adults should have their lipids checked before middle age. Patients with documented atherosclerosis and diabetes mellitus deserve the most scrutiny of their lipids since these patients are at the highest risk for suffering additional manifestations in the near term and thus



▲ Figure 28-1. Eruptive xanthomas on the arm of a man with untreated hyperlipidemia and diabetes mellitus. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

have the most to gain from lipid lowering. Additional risk reduction measures for atherosclerosis are discussed in Chapter 10; lipid lowering should be just one aspect of a program to reduce the progression and effects of atherosclerosis.

The best screening and treatment strategy for adults who do not have ASCVD is less clear. Several algorithms have been developed to guide the clinician in treatment decisions, but management decisions must always be individualized based on the patient's risk to maximize net benefit.

The 2018 American Heart Association/American College of Cardiology (AHA/ACC)/Multi-society guidelines recommend screening of all adults aged 20 years or older for high blood cholesterol. The 2016 United States Preventive Services Task Force (USPSTF) guidelines recommend beginning at age 20 years only if there are other cardiovascular risk factors such as tobacco use, diabetes, hypertension, obesity, or a family history of premature CVD. For men without other risk factors, screening is recommended beginning at age 35 years. For women and for men aged 20 to 35 without increased risk, the USPSTF makes no recommendation for or against routine screening for lipid disorders. Although there is no established interval for screening, screening can be repeated every 5 years for those with average or low risk and more often for those whose levels are close to therapeutic thresholds.

Individuals without CVD should have their 10-year risk of CVD calculated, with lifetime risk also considered. Although those with LDL cholesterol greater than 190 mg/dL (4.91 mmol/L) are recommended for treatment independent of their 10-year risk of CVD, all other patients are recommended for treatment based on their overall cardiovascular risk. While other calculators (such as SCORE or QRISK) may be more appropriate for other parts of the world, the best method for estimating 10-year risk in the United States is the Pooled Cohort Equations. First introduced in the 2013 ACC/AHA guidelines, the Pooled Cohort Equations include separate equations for White and Black patients and estimate the 10-year risk of heart attack, stroke, and cardiovascular death. This represents an improvement over the older Framingham 10-year calculator, which includes CHD but not stroke risk. The ACC/AHA risk estimator can be found at <http://www.cvriskcalculator.com/>, and mobile apps are available for download. While it has been shown to overestimate risk in some modern populations, including those with at least moderate socioeconomic status, the ACC/AHA risk estimator remains an excellent starting point for a risk discussion. Recalibrated versions of the calculator are available for countries across the world. The LIFE-CVD model is the best for illustrating lifetime risk and benefit of therapy (<https://www.u-prevent.com/en-GB/HealthyCalculator/HealthyCalculator>).

Shared decision making is a central part of cholesterol management in primary prevention. Therefore, the 2018 AHA/ACC/Multi-society guidelines and the 2019 ACC/AHA primary prevention guidelines identify a set of “**risk-enhancing factors**” that might influence a clinician and patient to favor cholesterol-lowering treatment. Table 28–1

Table 28–1. Risk-enhancing factors that help identify patients who may benefit most from lipid-lowering therapy: 2018 AHA/ACC/Multi-society guidelines.

Family history of premature disease (males, age < 55 years; females, age < 65 years)
Primary hypercholesterolemia (LDL cholesterol, 160–189 mg/dL [4.1–4.8 mmol/L]; non-HDL cholesterol, 190–219 mg/dL [4.9–5.6 mmol/L])
Metabolic syndrome
Chronic kidney disease (not end-stage kidney disease)
Chronic inflammatory conditions, such as psoriasis, rheumatoid arthritis, or HIV/AIDS
History of preeclampsia or of premature menopause before age 40 years
High-risk race/ethnicities (eg, South Asian ancestry)
Persistently high triglycerides \geq 175 mg/dL
Elevated high-sensitivity C-reactive protein (\geq 2.0 mg/L)
Elevated lipoprotein(a) (\geq 50 mg/dL or \geq 125 nmol/L)
Elevated apolipoprotein B (\geq 130 mg/dL)
Ankle brachial index < 0.9

lists these risk-enhancing factors that may be considered, particularly for patients at borderline to intermediate risk (5–20% 10-year cardiovascular risk).

Importantly, the 2018 AHA/ACC/Multi-society guidelines and the 2019 ACC/AHA primary prevention guidelines also identify the **coronary artery calcium score** as the single best test for additional risk stratification. The coronary calcium score is a simple noncontrast cardiac-gated CT scan that takes about 10–15 minutes to do, is associated with approximately 1 mSv of radiation, and costs between \$50 and \$300, although some centers have begun offering the test for free. As opposed to the risk-enhancing factors, which may incline a clinician and patient toward treatment, the coronary artery calcium score may also help identify patients who are unlikely to benefit from cholesterol-lowering therapy. For example, when the coronary artery calcium score is zero in the absence of smoking or diabetes, the patient is low risk and less likely to receive net benefit from therapy; instead, the coronary artery calcium score can be repeated in approximately 3 years for higher-risk patients and 7 years for lower-risk patients. In 2021, the National Lipid Association published a comprehensive clinical practice statement on coronary artery calcium testing. The USPSTF does not endorse calcium scoring as a broad screening test; rather it says the test should be reserved for situations in which additional data will inform shared decision making and potentially change a therapeutic decision.

Statins are nearly always the first-line therapy. Treatment decisions are based on the presence of clinical CVD or diabetes, LDL cholesterol greater than 190 mg/dL (4.91 mmol/L), patient age, and the estimated 10-year risk of developing CVD. The 2018 AHA/ACC/Multi-society guidelines define four groups of patients who benefit from statin medications: (1) individuals with clinical ASCVD; (2) individuals with primary elevation of LDL cholesterol greater than 190 mg/dL (4.91 mmol/L); (3) individuals aged 40–75 with diabetes and LDL greater than or equal to 70 mg/dL (1.81 mmol/L); and

(4) individuals aged 40–75 without clinical ASCVD or diabetes, with LDL 70–189 mg/dL (1.81–4.91 mmol/L), and estimated 10-year CVD risk of 7.5% or higher.

Ezetimibe and PCSK9 inhibitors have the strongest recommendations as second-line therapy for patients with (1) CVD whose LDL on statin therapy remains above the 70 mg/dL treatment threshold or (2) possible familial hypercholesterolemia with baseline LDL greater than 190 mg/dL (4.91 mmol/L) whose LDL remains above the 100 mg/dL treatment threshold. In high-risk patients, ezetimibe therapy is favored in part due to reduced cost, while in very high-risk patients, PCSK9 inhibitor therapy should be considered.

► Screening & Treatment in Older Patients

Meta-analysis of evidence relating cholesterol to CVD in older adults suggests that cholesterol is a somewhat weaker risk factor for CVD for persons over age 75 years. The 2018 AHA/ACC/Multi-society guidelines suggest continuing statin treatment in patients over age 75 who have CVD. The guidelines, however, suggest selectively treating patients over the age of 75 who do not have evidence of CVD. Individual patient decisions to discontinue statin therapy should be based on overall functional status and life expectancy, comorbidities, and patient preference and should be made in context with overall therapeutic goals and end-of-life decisions.

- Arnett DK et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2019;74:1376. [PMID: 30894319]
- Cardoso R et al. Selective use of coronary artery calcium testing for shared decision making: guideline endorsed and ready for prime time. *Ann Intern Med.* 2019;170:262. [PMID: 30743262]
- Dzaye O et al. Warranty period of a calcium score of zero: comprehensive analysis from the Multiethnic Study of Atherosclerosis. *JACC Cardiovasc Imaging.* 2021;14:990. [Epub ahead of print] [PMID: 33129734]
- Greenland P et al. Coronary calcium score and cardiovascular risk. *J Am Coll Cardiol.* 2018;72:434. [PMID: 30025580]
- Grundy SM et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary. *Circulation.* 2019;139:e1046. [PMID: 30565953]
- Jaspers NEM et al. Prediction of individualized lifetime benefit from cholesterol lowering, blood pressure lowering, anti-thrombotic therapy, and smoking cessation in apparently healthy people. *Eur Heart J.* 2020;41:1190. [PMID: 31102402]
- Mach F et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J.* 2020;41:111. [PMID: 31504418]
- Michos ED et al. Lipid management for the prevention of atherosclerotic cardiovascular disease. *N Engl J Med.* 2019;381:1557. [PMID: 31618541]
- Orringer CE, Blaha MJ et al. The National Lipid Association scientific statement on coronary artery calcium scoring to guide preventive strategies for ASCVD risk reduction. *J Clin Lipidol.* 2021;15:33. [PMID: 33419719]
- Wang N et al. Intensive LDL cholesterol-lowering treatment beyond current recommendations for the prevention of major vascular events: a systematic review and meta-analysis of randomised trials including 327 037 participants. *Lancet Diabetes Endocrinol.* 2020;8:36. [PMID: 31862150]

TREATMENT OF HIGH LDL CHOLESTEROL

Reduction of LDL cholesterol with statins is just one part of a program to reduce the risk of CVD. Other measures—including diet, exercise, smoking cessation, hypertension control, diabetes control, and antithrombotic therapy—are also of central importance. For example, exercise (and weight loss) may reduce the LDL cholesterol and increase the HDL.

The use of medications to raise the HDL cholesterol has not been demonstrated to provide additional benefit. For example, cholestrylo ester transfer protein inhibitors are a class of medicines being investigated to raise HDL levels; however, agents in this class have not been shown to be effective in so doing. The addition of niacin to statins has also been carefully studied in the AIM-HIGH study and the HPS2-THRIVE study in patients at high risk for CVD and shown not to produce any further benefit (ie, to decrease parameters of cardiovascular risk).

- Pappa E et al. Cardioprotective properties of HDL: structural and functional considerations. *Curr Med Chem.* 2020;27:2964. [PMID: 30714519]
- van der Vorst EPC. High-density lipoproteins and apolipoprotein A1. *Subcell Biochem.* 2020;94:399. [PMID: 32189309]

► Diet Therapy

Studies of nonhospitalized adults have reported only modest cholesterol-lowering benefits of individual dietary therapies, typically in the range of a 5–10% decrease in LDL cholesterol, and even less over the long term. The effect of diet therapies, however, may be additive; some patients will have striking reductions in LDL cholesterol—up to a 25–30% decrease—whereas others will have clinically important increases. Thus, the results of diet therapy should be assessed about 4 weeks after initiation.

Several nutritional approaches to diet therapy are available. Most Americans currently eat over 35% of calories as fat, of which 15% is saturated fat. A traditional cholesterol-lowering diet recommends reducing total fat to 25–30% and saturated fat to less than 7% of calories, with complete elimination of trans fats. These diets replace fat, particularly saturated fat, with carbohydrate. Other diet plans, including the Dean Ornish Diet and most vegetarian diets, restrict fat even further. Low-fat, high-carbohydrate diets may, however, result in insulin resistance and reductions in HDL cholesterol.

An alternative strategy is the Mediterranean diet, which maintains total fat at approximately 35–40% of total calories but replaces saturated fat with monounsaturated fat such as that found in canola oil and in olives, peanuts, avocados, and their oils. This diet is equally effective at lowering LDL cholesterol, and is less likely to lead to reductions in HDL cholesterol. Several studies have suggested that this diet may also be associated with reductions in endothelial dysfunction, insulin resistance, and markers of vascular inflammation and may result in better resolution of the metabolic syndrome than traditional cholesterol-lowering diets. A clinical trial demonstrated reduced

cardiovascular events in persons on a Mediterranean diet supplemented with additional nuts or extra-virgin olive oil compared to persons on a less intensive standard Mediterranean diet.

Other dietary changes may also result in beneficial changes in blood lipids. Soluble fiber, such as that found in oat bran or psyllium, may reduce LDL cholesterol by 5–10%. Plant stanols and sterols can reduce LDL cholesterol by 10%. Intake of garlic, soy protein, vitamin C, and pecans may also yield modest reductions of LDL cholesterol. Because oxidation of LDL cholesterol is a potential initiating event in atherosclerosis, diets rich in antioxidants, found primarily in fruits and vegetables, may be helpful (see Chapter 29). Studies have suggested that when all of these elements are combined into a single dietary prescription, the impact of diet on LDL cholesterol may approach that of statin medications, lowering LDL cholesterol by close to 30%.

- Abdelhamid AS et al. Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2018;7:CD012345. [PMID: 30019767]
- Arnett DK et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019;74:1376. [PMID: 30894319]
- Grundy SM et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary. Circulation. 2019;139:e1046. [PMID: 30565953]
- Pallazola VA et al. A clinician's guide to healthy eating for cardiovascular disease prevention. Mayo Clin Proc Innov Qual Outcomes. 2019;3:251. [PMID: 31485563]

Table 28-2. Indications for high-intensity and moderate-intensity statins: recommendations of the 2018 AHA/ACC/Multi-society guidelines.

Indications	Treatment Recommendation
Presence of clinical ASCVD	High-intensity statin or moderate-intensity statin if over age 75 years
Primary elevation of LDL cholesterol ≥ 190 mg/dL (4.91 mmol/L)	High-intensity statin
Age 40–75 years ¹ Presence of diabetes LDL ≥ 70 mg/dL (1.81 mmol/L)	Moderate-intensity statin or high-intensity statin if 10-year CVD risk $\geq 7.5\%$ or other risk-enhancing criteria ¹
Aged 40–75 years No clinical ASCVD or diabetes LDL 70–189 mg/dL (1.81–4.91 mmol/L) Estimated 10-year CVD risk $\geq 7.5\%$ or coronary artery calcium > 0 and $>$ 75th percentile	Treat with moderate- to high-intensity statin

¹Diabetes duration > 10 years, microalbuminuria, chronic kidney disease, and ankle brachial index < 0.9 favor aggressive treatment even for patients age 20–39 years.

AHA/ACC, American Heart Association/American College of Cardiology; ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

► Pharmacologic Therapy

There are eight classes of medications currently available for consideration in patients who require drug treatment of an elevated cholesterol (statins, ezetimibe, PCSK9 inhibitors, omega-3 fatty acids, bempedoic acid, bile-acid-binding resins, fibrates, and niacin). As discussed above, statins are the cornerstone of nearly all medical regimens, and current guidelines define four groups of patients who benefit from statin medications (adults with diabetes mellitus, those with existing ASCVD, LDL cholesterol greater than 190 mg/dL, or 10-year risk of ASCVD greater than 7.5%). For LDL cholesterol, the evidence is strongest for ezetimibe and PCSK9 inhibitors; for triglycerides, the evidence is strongest for adding prescription-grade omega-3 fatty acid preparations. There is less evidence for cholesterol absorption inhibitors, fibrates, and niacin. Bempedoic acid, an inhibitor of adenosine triphosphate citrate lyase (ACL)—the enzyme two steps upstream from HMG-CoA reductase, the target of statins—was approved by the FDA in 2020 and represents a new option for additional LDL lowering.

A. Statins (Hydroxymethylglutaryl-Coenzyme A [HMG-CoA] Reductase Inhibitors)

The statins (HMG-CoA reductase inhibitors) work by inhibiting the rate-limiting enzyme in the formation of

cholesterol. Cholesterol synthesis in the liver is reduced, with a compensatory increase in hepatic LDL receptors (so that the liver can take more of the cholesterol that it needs from the blood) and a reduction in the circulating LDL cholesterol level by 50% or more at the highest doses. There are also modest increases in HDL levels, substantial decreases in triglyceride levels, and marked reductions in high-sensitivity C-reactive protein levels.

The 2018 AHA/ACC/Multi-society guidelines divide statins into two categories: “high-intensity” and “moderate-intensity” statins (Table 28-2). High-intensity statins lower LDL cholesterol by approximately 50%. Examples include high-dose atorvastatin 40–80 mg/day and rosuvastatin 20–40 mg/day (Table 28-3). Moderate-intensity statins lower LDL cholesterol by approximately 30–50%. Examples include pitavastatin 2–4 mg/day, simvastatin 20–40 mg/day, and pravastatin 40–80 mg/day, as well as low-dose atorvastatin 10–20 mg/day and rosuvastatin 5–10 mg/day. All statins are given once daily in the morning or evening.

Statin-associated muscle aches, with normal serum creatine kinase levels, occur in up to 10% of patients, and often such patients can tolerate the statin upon rechallenge. The SAMSON trial demonstrated the importance of the nocebo effect with perceived statin intolerance (reported side effects being due to patient expectations); in this trial, 90% of the symptoms associated with statin rechallenge were also noted with placebo.

Table 28–3. Effects of selected lipid-modifying drugs (listed alphabetically).

Drug	Lipid-Modifying Effects		Triglyceride	Initial Daily Dose	Maximum Daily Dose	Cost for 30 Days of Treatment with Dose Listed ¹
	LDL	HDL				
Alirocumab (Praluent)	–45 to –60%	±	±	75 mg once every 2 weeks	150 mg once every 2 weeks	\$540.00 (75 mg every 2 weeks)
Atorvastatin (Lipitor)	–25 to –40%	+5 to 10%	↓↓	10 mg once	80 mg once	\$8.49 (20 mg once)
Bempedoic acid (Nexletol)	–17–20%	–6%	±	180 mg once	180 mg once	\$419.76
Cholestyramine (Questran, others)	–15 to –25%	+5%	±	4 g twice a day	24 g divided	\$201.06 (8 g divided)
Colesevelam (WelChol)	–10 to –20%	+10%	±	625 mg, 6–7 tablets once	625 mg, 6–7 tablets once	\$673.82 (6 tablets once)
Colestipol (Colestid)	–15 to –60%	+5%	±	5 g twice a day	30 g divided	\$235.82 (10 g divided)
Evolocumab (Repatha)	–50 to –60%	±	±	140 mg once every 2 weeks	420 mg once monthly	\$571.86 (140 mg every 2 weeks)
Ezetimibe (Zetia)	–20%	+5%	±	10 mg once	10 mg once	\$250.80 (10 mg once)
Fenofibrate (Tricor, others)	–10 to –15%	+15 to 25%	↓↓	48 mg once	145 mg once	\$37.20 (145 mg once)
Fenofibric acid (Trilipix)	–10 to –15%	+15 to 25%	↓↓	45 mg once	135 mg once	\$160.05 (135 mg once)
Fluvastatin (Lescol)	–20 to –30%	+5 to 10%	↓	20 mg once	40 mg once	\$113.40 (20 mg once)
Gemfibrozil (Lopid, others)	–10 to –15%	+15 to 20%	↓↓	600 mg once	1200 mg divided	\$58.20 (600 mg twice a day)
Lomitapide (Juxtapid) ^{2,3}	–40 to –50% ⁴	–7% ⁴	↓↓	5 mg once	60 mg once	\$55,802.55 (any dose)
Lovastatin (Mevacor, others)	–25 to –40%	+5 to 10%	↓	10 mg once	80 mg divided	\$67.50 (20 mg once)
Niacin (OTC, Niaspan)	–15 to –25%	+25 to 35%	↓↓	100 mg once	3–4.5 g divided	\$5.40 (1.5 g twice a day, OTC) \$282.60 (2 g Niaspan)
Omega-3 fatty acid ethyl esters (Lovaza)			↓↓	4 g once	4 g once	\$248.40 (4 g daily)
Omega-3 fatty acid icosapent ethyl (Vascepa)			↓↓	2 g twice	2 g twice	\$376.80 (2 g twice day)
Pitavastatin (Livalo, Zypitamag)	–30 to 40%	+10 to 25%	↓↓	2 mg once	4 mg once	\$279.00 (2 mg once)
Pravastatin (Pravachol)	–25 to –40%	+5 to 10%	↓	20 mg once	80 mg once	\$75.00 (20 mg once)
Rosuvastatin (Crestor)	–40 to –50%	+10 to 15%	↓↓	10 mg once	40 mg once	\$43.20 (20 mg once)
Simvastatin (Zocor, others)	–25 to –40%	+5 to 10%	↓↓	5 mg once	80 mg once	\$3.90 (10 mg once)

¹Average wholesale price (AWP, for AB-rated generic when available) for quantity listed. Source: IBM Micromedex Red Book (electronic version), IBM Watson Health, Greenwood Village, CO, USA. Available at <https://www.micromedexsolutions.com> (cited April 18, 2021). AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions.

²Restricted to patients with homozygous familial hypercholesterolemia.

³FDA Black Box warning regarding hepatotoxicity.

⁴62% of patients also received plasma lipoprotein apheresis.

⁵No plasma lipoprotein apheresis allowed in clinical trial.

HDL, high-density lipoprotein; LDL, low-density lipoprotein; ± variable, if any; others, indicates availability of less expensive generic preparations; OTC, over the counter.

The Statin-Associated Muscle Symptom Clinical Index (SAMS-CI) is a useful tool to help differentiate statin-related symptoms from symptoms unrelated to statins. More serious, but very uncommon, muscle disease includes myositis and rhabdomyolysis, with moderate and marked elevations of serum creatine kinase levels, respectively. Such muscle disease occurs more often when the statin is taken with niacin or a fibrate, as well as with erythromycin, antifungal medications, nefazodone, or cyclosporine. Simvastatin at the highest approved dose (80 mg) is associated with an elevated risk of muscle injury or myopathy; this dose should be used only in patients who have been taking simvastatin at a lower dose for longer than 1 year without muscle toxicity. Liver disease, with elevations of serum transaminases, is another uncommon side effect of statin therapy and is again more common in patients who are also taking fibrates or niacin. Manufacturers of statins recommend monitoring liver enzymes before initiating therapy and as clinically indicated thereafter; current guidelines do not recommend routine monitoring. Liver failure can occur but is extremely uncommon. Finally, statin therapy is associated with a 10% increase in risk of developing diabetes mellitus in at-risk individuals (eg, those with the metabolic syndrome).

B. Ezetimibe

Ezetimibe inhibits the intestinal absorption of dietary and biliary cholesterol across the intestinal wall by inhibiting a cholesterol transporter. The dose of ezetimibe is 10 mg/day orally. Ezetimibe reduces LDL cholesterol between 15% and 20% when used as monotherapy, reduces high-sensitivity C-reactive protein, and can further reduce LDL in patients taking statins in whom the therapeutic goal has not been reached. While beneficial effects of ezetimibe monotherapy on cardiovascular outcomes are available from only a large open-label trial, the double-blind IMPROVE-IT trial showed that adding ezetimibe to a statin resulted in a small incremental 5–10% relative risk reduction in detrimental cardiovascular outcomes. At the end of 7 years of study, patients taking ezetimibe-simvastatin had a 2% absolute reduction in cardiovascular events compared to patients taking simvastatin alone. Current guidelines recommend adding ezetimibe therapy to maximally tolerated statin therapy in patients at high risk for CVD whose LDL cholesterol remains above the treatment threshold of 70 mg/dL.

C. Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors

As of early 2021, available PCSK9 inhibitors are fully human monoclonal antibodies that inhibit PCSK9-mediated LDL-receptor degradation and lower LDL cholesterol levels by 50–60% and lipoprotein(a) by up to 20–30%. Two agents, alirocumab and evolocumab, are approved for use in the United States for patients with familial hypercholesterolemia or patients with CVD who require additional lowering of LDL cholesterol. The medications are injected subcutaneously every 2–4 weeks. No significant increase in adverse events has been observed compared to placebo. The FOURIER

(Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial compared evolocumab with placebo in 27,564 patients with established atherosclerotic disease already taking statin therapy; participants were monitored for a median of 2.2 years. LDL cholesterol was reduced by 59%. Patients receiving the evolocumab plus statin had a 15% reduction in the primary composite endpoint of cardiovascular death, myocardial infarction, stroke, hospital admission for unstable angina, or coronary revascularization and a 20% reduction in the secondary outcome of cardiovascular death, myocardial infarction, or stroke. The ODYSSEY-OUTCOMES study randomized 18,924 patients with recent acute coronary syndrome to alirocumab or placebo, demonstrating a 15% reduction in the primary composite cardiovascular endpoint and a 15% reduction in all-cause mortality in secondary statistical testing after median 2.8-year follow-up.

However, despite encouraging results from multiple clinical trials, initial cost-effectiveness models suggested that PCSK9 inhibitors were not cost-effective. After marked price reductions in 2018 and 2019, PCSK9 inhibitors are closer to being cost-effective; however, guidelines suggest that their relatively high cost must still remain part of the consideration regarding their use. Current guidelines recommend addition of PCSK9 inhibitors to statins at maximally tolerated doses in patients at very high risk for CVD when on-treatment LDL cholesterol remains above 70 mg/dL (or above 100 mg/dL in patients with familial hypercholesterolemia). Patients considered to be at very high-risk for CVD include those with recent acute coronary syndrome within 12 months; multiple prior myocardial infarctions or strokes; significant unrevascularized coronary artery disease; and polyvascular disease (coronary plus cerebrovascular or peripheral vascular disease).

D. Omega-3 Fatty Acid Preparations

Omega-3 fatty acids are essential fatty acids that must be consumed in the diet and are a prominent feature of Mediterranean-style diets. In pharmacologic doses, omega-3 fatty acid preparations can lower triglycerides by up to 30%, with modest reductions in apolipoprotein-B-containing lipoproteins and high-sensitivity C-reactive protein. Pharmacologic therapy should be differentiated from dietary omega-3 fatty acid supplements. The former is an FDA-approved product usually given at a much higher dose; dietary supplements are variable, the supporting evidence is much weaker, and they are not currently regulated.

There is modest evidence from meta-analyses that omega-3 fatty acid supplementation reduces myocardial infarctions, though with no reduction in total or cardiovascular mortality. Omega-3 ethyl esters have not been associated with cardiovascular event reduction when added to statin therapy.

In contrast, icosapent ethyl, which is a highly purified eicosapentaenoic acid (EPA) only preparation, was shown to reduce cardiovascular deaths, nonfatal myocardial infarctions, nonfatal strokes, coronary revascularizations, and unstable angina by 25% in statin-treated patients with triglycerides greater than 135 mg/dL in the 8179 person

REDUCE-IT randomized clinical trial compared to a mineral oil placebo. The mechanism of action of icosapent ethyl is not yet clear but likely involves multiple mechanisms beyond lipid lowering, including antiplatelet activity, anti-inflammatory activity, and arrhythmia prevention. In 2019, the FDA granted icosapent ethyl a broad indication for CVD event lowering in patients with triglycerides over 150 mg/dL and either established CVD or diabetes mellitus plus two or more additional risk factors for CVD. There remains controversy about the efficacy of omega-3 therapies, since the 2020 STRENGTH trial showed no CVD benefit of omega-3 carboxylic acids; it remains unclear if this result was due to a different omega-3 fatty acid preparation, chance, or a much smaller benefit of omega-3 fatty acids preparations than originally demonstrated.

E. Bempedoic Acid

Similar to statins, bempedoic acid targets cholesterol synthesis in the liver, ultimately resulting in upregulation of expression of the LDL receptor. Bempedoic acid is a small molecule inhibitor of adenosine triphosphate citrate lyase (ACL), an enzyme that is upstream of the mechanism of statins (inhibition of HMG-CoA reductase). Bempedoic acid lowers LDL approximately 17–20% on top of moderate to high intensity statins. Bempedoic acid is also marketed in combination with ezetimibe; this combination provides approximately 38% LDL reduction on top of background lipid-lowering therapy. Treatment with bempedoic acid may mildly decrease both high-sensitivity C-reactive protein (hsCRP) and the risk of diabetes. Patients treated with bempedoic acid should be monitored for hyperuricemia and the potential onset or worsening of gout. Bempedoic acid also appears to modestly increase the risk of tendon rupture. Bempedoic acid should not be used with more than 20 mg of simvastatin daily or 40 mg of pravastatin daily.

F. Bile Acid-Binding Resins

The bile acid-binding resins include cholestyramine, colestevam, and colestipol. In the pre-statin era, treatment with these agents reduced the incidence of coronary events in middle-aged men by about 20%, with no significant effect on total mortality. The resins work by binding bile acids in the intestine. The resultant reduction in the enterohepatic circulation causes the liver to increase its production of bile acids, using hepatic cholesterol. Thus, hepatic LDL receptor activity increases, with a decline in plasma LDL levels. The triglyceride level tends to increase in some patients treated with bile acid-binding resins; these resins should be used with caution in patients with elevated triglycerides and not at all in patients who have triglyceride levels above 500 mg/dL. The clinician can anticipate a reduction of 15–25% in the LDL cholesterol level, with insignificant effects on the HDL level. Resins are the only lipid-modifying medication considered safe in pregnancy.

These agents may interfere with the absorption of fat-soluble vitamins (thereby complicating the management of patients receiving warfarin) and may bind other drugs in

the intestine. They often cause gastrointestinal symptoms, such as constipation and gas. Concurrent use of psyllium may ameliorate these gastrointestinal side effects.

G. Fibric Acid Derivatives

The fibrates are peroxisome proliferative-activated receptor-alpha (PPAR-alpha) agonists that result in significant reductions of plasma triglycerides and increases in HDL cholesterol. They reduce LDL levels by about 10–15% (although the result is variable) and triglyceride levels by about 40% and raise HDL levels by about 15–20%. The fibric acid derivatives or fibrates approved for use in the United States are gemfibrozil and fenofibrate. Ciprofibrate and bezafibrate are also available for use internationally.

Gemfibrozil monotherapy reduced CHD rates in hypercholesterolemic middle-aged men free of coronary disease in the Helsinki Heart Study. The effect was observed only among those who also had lower HDL cholesterol levels and high triglyceride levels. In a Veterans Affairs study, gemfibrozil monotherapy was also shown to reduce cardiovascular events in men with existing CHD whose primary lipid abnormality was a low HDL cholesterol.

However, fibrates have not been shown to reduce cardiovascular events in all statin-treated patients with CVD or diabetes. For example, in the ACCORD study, addition of fenofibrate to statin in patients with diabetes and mild triglyceride elevations resulted in no benefit.

The usual dose of gemfibrozil is 600 mg once or twice a day. Side effects include cholelithiasis, hepatitis, and myositis. The incidence of the latter two conditions may be higher among patients also taking other lipid-lowering agents. Fenofibrate, 48–145 mg daily, has slightly fewer side effects than gemfibrozil.

H. Niacin (Nicotinic Acid)

Niacin reduces the production of VLDL particles, with secondary reduction in LDL and increases in HDL cholesterol levels. The average effect of full-dose niacin therapy is a 15–25% reduction in LDL cholesterol and a 25–35% increase in HDL cholesterol.

There is very little evidence to support the use of niacin in the modern era. In two large pivotal clinical trials, AIM-HIGH and HPS2-THRIVE, extended-release niacin did not reduce cardiovascular events when added to statin therapy in high-risk patients. Therefore, niacin should be rarely used.

Treatment Algorithms

For patients who require a lipid-modifying medication, an HMG-CoA reductase inhibitor (statin) is recommended. In patients with CVD, this should be at its maximally tolerated dose.

Combination therapy is indicated for (1) patients with familial hypercholesterolemia with on-treatment LDL cholesterol that is above 100 mg/dL; (2) patients with advanced subclinical atherosclerosis (coronary artery calcium scores greater than 300 or even greater than 1000) or existing CVD with on-treatment LDL cholesterol that remains above 70 mg/dL; and (3) many high-risk

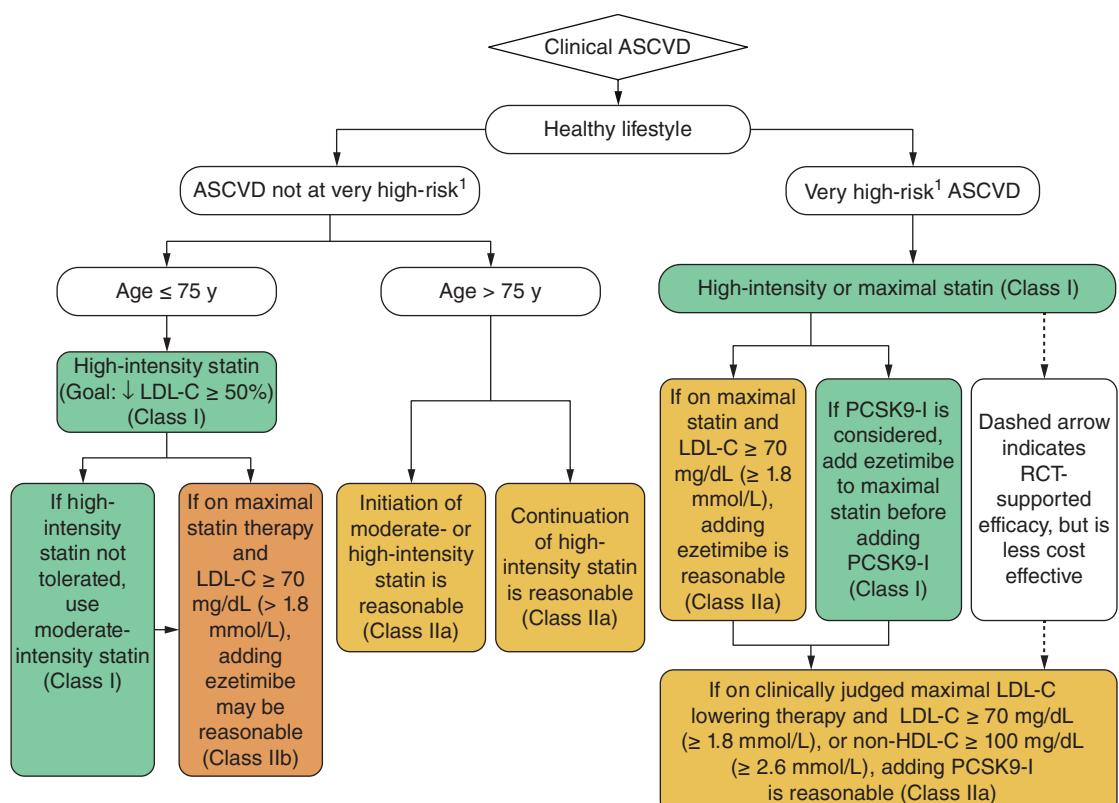
patients with triglycerides greater than 150 mg/dL or non-HDL cholesterol greater than 100 mg/dL.

Patients with heterozygous familial hypercholesterolemia or premature CVD may need two or more medications to get below the treatment threshold, while those without CVD (primary prevention) less commonly need multiple medications. The 2018 AHA/ACC/Multi-society guidelines recommend addition of ezetimibe in high-risk patients, while reserving PCSK9 inhibitor therapy for very high-risk patients or those taking maximally tolerated statin therapy and ezetimibe with LDL cholesterol still not below 70 mg/dL (Figure 28–2). Notably, the 2019 European Society of Cardiology guidelines have endorsed an LDL cholesterol treatment goal of less than 55 mg/dL in very high-risk patients, which uniquely include patients with at least two 50% coronary artery stenoses identified by coronary CT angiography. These guidelines further endorse an LDL goal of less than 40 mg/dL in the highest-risk patients with multiple recent CVD events. Other guidelines, including the American

Diabetes Association and the National Lipid Association, have endorsed the use of icosapent ethyl in high-risk patients with CVD or diabetes and on-treatment triglycerides greater than 150 mg/dL.

Patients with homozygous familial hypercholesterolemia may need plasmapheresis and/or special lipid-lowering therapies uniquely approved for this population (Table 28–3).

- Di Minno A et al. Efficacy and safety of bempedoic acid in patients with hypercholesterolemia: systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc.* 2020;9:e016262. [PMID: 32689862]
- Grundy SM et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary. *Circulation.* 2019;139:e1046. [PMID: 30565953]
- Mach F et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J.* 2020;41:111. [PMID: 31504418]



▲ **Figure 28–2.** Clinical treatment algorithm for patients with atherosclerotic cardiovascular disease (ASCVD). (Used, with permission, from Grundy SM et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary. *Circulation.* 2019;139:e1046. © 2018 American Heart Association, Inc.)

Nicholls SJ et al. Effect of high-dose omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk: the STRENGTH randomized clinical trial. *JAMA*. 2020;324:2268. [PMID: 33190147]

Ray KK et al. Pharmacological lipid-modification therapies for prevention of ischaemic heart disease: current and future options. *Lancet*. 2019;394:697. [PMID: 31448741]

Wood FA et al. N-of-1 trial of a statin, placebo, or no treatment to assess side effects. *N Engl J Med*. 2020;383:2182. [PMID: 33196154]

levels may also be helpful. In patients with fasting triglycerides greater than or equal to 500 mg/dL (5 mmol/L) despite adequate dietary compliance—and certainly in those with a previous episode of pancreatitis—therapy with a triglyceride-lowering drug (eg, statins, omega-3 preparations, or fibric acid derivatives) is indicated. Combinations of these medications may also be used.

Currently, drug treatment for patients with triglycerides greater than 150 mg/dL (1.5 mmol/L) is reserved for those with established CVD with well-controlled LDL cholesterol on maximally tolerated therapy with statins or other agents. Currently, data are strongest for icosapent ethyl.

HIGH BLOOD TRIGLYCERIDES

Patients with very high levels of serum triglycerides (greater than 1000 mg/dL) are at risk for pancreatitis. The pathophysiology is not certain, since pancreatitis never develops in some patients with very high triglyceride levels. Most patients with congenital abnormalities in triglyceride metabolism present in childhood; hypertriglyceridemia-induced pancreatitis first presenting in adults is more commonly due to an acquired problem in lipid metabolism.

Although there are no clear triglyceride levels that predict pancreatitis, most clinicians treat fasting levels above 500 mg/dL (5 mmol/L). The risk of pancreatitis may be more related to the triglyceride level following consumption of a fatty meal. Because postprandial increases in triglyceride are inevitable if fat-containing foods are eaten, fasting triglyceride levels in persons prone to pancreatitis should be kept well below that level.

The primary therapy for high triglyceride levels is dietary, avoiding alcohol, simple sugars, refined starches, and saturated and trans fatty acids, and restricting total calories. Control of secondary causes of high triglyceride

Bhatt DL et al; REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. 2019;380:11. [PMID: 30415628]

Chaudhry R et al. Pharmacological treatment options for severe hypertriglyceridemia and familial chylomicronemia syndrome. *Expert Rev Clin Pharmacol*. 2018;11:589. [PMID: 29842811]

Nurmohamed NS et al. Targeting apoC-III and ANGPTL3 in the treatment of hypertriglyceridemia. *Expert Rev Cardiovasc Ther*. 2020;18:355. [PMID: 32511037]

Orringer CE et al. National Lipid Association Scientific Statement on the use of icosapent ethyl in statin-treated patients with elevated triglycerides and high or very-high ASCVD risk. *J Clin Lipidol*. 2019;13:860. [PMID: 31787586]

Packard CJ et al. Causes and consequences of hypertriglyceridemia. *Front Endocrinol (Lausanne)*. 2020;11:252. [PMID: 32477261]

Rygiel K. Hypertriglyceridemia—common causes, prevention and treatment strategies. *Curr Cardiol Rev*. 2018;14:67. [PMID: 29366425]

Simha V. Management of hypertriglyceridemia. *BMJ*. 2020;371:m3109. [PMID: 33046451]

Nutritional Disorders & Obesity

Katherine H. Saunders, MD
Leon I. Igel, MD, FACP, FTOS

29

NUTRITIONAL DISORDERS

PROTEIN–ENERGY MALNUTRITION



ESSENTIALS OF DIAGNOSIS

- ▶ Decreased intake of energy or protein, increased nutrient losses, or increased nutrient requirements.
- ▶ **Kwashiorkor:** caused by protein deficiency.
- ▶ **Marasmus:** caused by combined protein and energy deficiency.
- ▶ Protein loss correlates with weight loss: 35–40% total body weight loss can be fatal.

General Considerations

Protein–energy malnutrition occurs as a result of a relative or absolute deficiency of energy and protein. It may be primary, due to inadequate food intake, or secondary, as a result of other illness. For many developing nations, primary protein–energy malnutrition remains a significant health problem. It occurs in two distinct syndromes. **Kwashiorkor**, caused by a deficiency of protein in the presence of adequate energy, is typically seen in weaning infants where foods containing protein are insufficient. **Marasmus**, caused by combined protein and energy deficiency, is seen where adequate quantities of food are not available.

In industrialized societies, protein–energy malnutrition is most often secondary to other diseases. **Kwashiorkor-like secondary protein–energy malnutrition** occurs primarily in hypermetabolic acute illnesses such as trauma, burns, and sepsis. **Marasmus-like secondary protein–energy malnutrition** typically results from chronic diseases such as chronic obstructive pulmonary disease (COPD), heart failure, cancer, or AIDS. In both syndromes, protein–energy malnutrition is caused either by decreased intake of energy and protein or by increased nutrient losses related to underlying illness. For example, diminished energy intake may result from poor dentition or various gastrointestinal disorders. Increased nutrient

losses may result from malabsorption, diarrhea, and glycosuria. Increased nutrient requirements occur with fever, surgery, neoplasia, and burns.

Clinical Findings

Clinical manifestations of protein–energy malnutrition range from mild growth retardation and weight loss to a number of distinct clinical syndromes. In the developing world, children manifest marasmus and kwashiorkor. In industrialized nations, clinical manifestations of secondary protein–energy malnutrition are affected by the patient's nutritional status prior to illness, the illness resulting in the protein and energy deficiency, and degree of the deficiency.

In most patients with marasmus-like secondary protein–energy malnutrition, wasting begins with weight loss that progresses to severe cachexia. In the most severe form of this disorder, body fat stores disappear and muscle mass decreases, most noticeably in the temporalis and interosseous muscles. Laboratory studies may be unremarkable—serum albumin, for example, may be normal or slightly decreased, but rarely to less than 2.8 g/dL (28 g/L). In contrast, kwashiorkor-like secondary protein–energy malnutrition—with its rapidity of onset—may develop in patients with normal subcutaneous fat and muscle mass and even in patients with excess fat and muscle. The serum protein level, however, typically declines and serum albumin is often less than 2.8 g/dL (28 g/L). Dependent edema, ascites, or anasarca may develop. As with primary protein–energy malnutrition, combinations of the marasmus-like and kwashiorkor-like syndromes can occur simultaneously, typically in patients with progressive chronic disease in whom a superimposed acute illness develops.

Treatment

The treatment of severe protein–energy malnutrition is a slow process requiring great care. Initial efforts should be directed at correcting fluid and electrolyte abnormalities and infections. Of particular concern are depletion of potassium, magnesium, and calcium as well as acid–base abnormalities. The second phase of treatment is directed at repletion of protein, energy, and micronutrients. Treatment is started with modest quantities of protein and calories calculated based on the patient's actual body weight. Adult

patients are given 1 g/kg of protein and 30 kcal/kg of calories per day. Concomitant administration of vitamins and minerals is obligatory. Either the enteral or parenteral route can be used, although the former is preferable. Patients with less severe protein–calorie undernutrition can be given calories and protein simultaneously with the correction of fluid and electrolyte abnormalities.

Patients treated for protein–energy malnutrition require close follow-up. In adults, both calories and protein are advanced as tolerated to 30–35 kcal/kg/day and 1.5 g/kg/day of protein.

Patients who are refed too rapidly may develop a number of untoward clinical sequelae. During refeeding, circulating potassium, magnesium, phosphorus, and glucose move intracellularly and can result in low serum levels of each, sometimes with significant consequences. The administration of water and sodium with carbohydrate refeeding can result in heart failure in persons with depressed cardiac function. Enteral refeeding can lead to diarrhea and malabsorption due to small intestinal mucosal atrophy.

Refeeding edema is benign but must be differentiated from heart failure. Changes in renal sodium reabsorption and poor skin and blood vessel integrity may result in dependent edema without other signs of heart disease. Treatment includes elevation of the dependent area and modest sodium restriction. Diuretics are usually ineffective, may aggravate electrolyte deficiencies, and should not be used.

The prevention and early detection of protein–energy malnutrition in hospitalized patients require awareness of its risk factors and early symptoms and signs. Patients at risk require formal assessment of nutritional status and close observation of dietary intake, body weight, and nutritional requirements during the hospital stay.

- Reber E et al. Nutritional risk screening and assessment. *J Clin Med.* 2019;8:E1065. [PMID: 31330781]
 Sieber CC. Malnutrition and sarcopenia. *Aging Clin Exp Res.* 2019;31:793. [PMID: 31148100]
 Volkert D et al. ESPEN guideline on clinical nutrition and hydration in geriatrics. *Clin Nutr.* 2019;38:10. [PMID: 30005900]

OBESITY

ESSENTIALS OF DIAGNOSIS

- Disorder of energy homeostasis; body mass index (BMI) > 30 kg/m².
- Upper body obesity (abdomen and flank) of greater health consequence than lower body obesity (buttocks and thighs).
- Associated comorbid conditions include type 2 diabetes mellitus, hypertension, hyperlipidemia, heart disease, stroke, and obstructive sleep apnea.

► Definition & Measurement

Obesity is a multifactorial, chronic disease characterized by an accumulation of visceral and subcutaneous fat, which promotes adipocyte dysfunction. Obesity predisposes to a

wide variety of comorbid conditions. **BMI** typically correlates with excess adipose tissue. It is calculated by dividing body weight in kilograms by height in meters squared. The National Institutes of Health (NIH) defines a normal BMI as 18.5–24.9 kg/m². Overweight is defined as BMI 25–29.9 kg/m². Class I obesity is 30–34.9 kg/m², class II is 35–39.9 kg/m², and class III is greater than or equal to 40 kg/m². Upper body obesity (excess adipose tissue around the waist and flank) is a greater health hazard than lower body obesity (adipose tissue in the thighs and buttocks). Patients with obesity and increased abdominal circumference (greater than 102 cm or 40 inches in men and 88 cm or 35 inches in women) or high waist–hip ratios (greater than 1.0 in men and 0.85 in women) have a greater risk of weight-related comorbid conditions and early death than patients with the same BMI and lower ratios. Visceral fat within the abdominal cavity is more hazardous to health than subcutaneous fat around the abdomen. Survey data suggest that almost 40% of Americans have obesity.

► Etiology

Both genetic and environmental factors contribute to the development of obesity. Twin studies demonstrate that genetics account for 40–90% of the variation in BMI, although only a small percentage is due to single gene mutations. Most obesity develops from interactions of multiple genes, environmental factors, and behavior. The rapid increase in obesity in the last several decades points to major roles for environmental and behavioral factors.

► Medical Evaluation of the Patient with Obesity

Medical history should determine the age at onset of weight gain, recent weight changes, family history of obesity, occupational history, eating and exercise behavior, previous weight loss experience, and psychosocial factors including assessment for depression and eating disorders.

Physical examination should assess BMI, degree and distribution of body fat, and overall nutritional status. Signs of secondary causes of obesity should be pursued; however, less than 1% of patients have an identifiable cause. Cushing syndrome is an example that can be diagnosed by physical examination and laboratory testing in patients with unexplained recent weight gain (see Chapter 26). All patients should be screened for weight-related comorbid conditions, including obstructive sleep apnea. Blood pressure, waist circumference, fasting glucose, comprehensive metabolic profile, lipid panel, and hemoglobin A_{1c} should be measured as well as other laboratory tests as clinically indicated.

► Treatment

Weight loss of 5–10% body weight is sufficient in many patients with obesity for clinically relevant improvements in many risk factors, and the risk reduction appears to be “dose-related.” Magnitude of weight loss at 1 year is strongly associated with improvements in many parameters including blood sugar, blood pressure, triglycerides, and high-density lipoprotein (HDL) cholesterol.

Successful treatment of obesity requires a multidisciplinary approach to counteract the body's resistance to

weight loss. Diet, physical activity, and behavioral modifications are the cornerstones of weight management. Many **dietary strategies** can be effective for weight loss. Recommendations should be tailored to a patient's preferences as dietary adherence is associated with greater weight loss and greater reductions in cardiac risk factors. Dietary instructions should emphasize intake of predominantly "unprocessed" foods, with special attention to limiting foods that provide large amounts of calories without other nutrients, eg, ultra-processed foods, sugary drinks, fast food, junk food, and sweets. A Mediterranean diet can be a good option for patients at high cardiovascular risk, since it has been shown to reduce the incidence of major cardiovascular events. A low-glycemic-index diet can curb hunger and decrease cravings by reducing blood sugar fluctuations. Meal replacement diets can also achieve effective weight loss. Registered dietitians can provide dietary education and customize diet plans.

Long-term changes in eating behavior are required to maintain weight loss and formal **behavior modification** programs are available. It is important to emphasize planning and self-monitoring, including weighing at regular intervals and keeping a food log to track caloric intake. Self-monitoring aids in behavioral change and provides the practitioner with additional data from which to tailor recommendations. Patients can learn to recognize "eating cues" (emotional, situational, etc) and how to avoid or control them. Weight maintenance can be more challenging than initial weight loss, hence it is important to continue self-monitoring and regular follow-up to ensure adherence to the treatment plan.

Physical activity offers several advantages for patients trying to achieve and maintain weight loss. Aerobic exercise increases daily energy expenditure and partially prevents the decrease in basal energy expenditure (BEE) resulting from weight loss. It is particularly useful for long-term weight maintenance and helps preserve lean body mass. Exercise plus diet results in slightly greater weight loss than diet or exercise alone. A greater intensity of exercise is associated with a greater amount of weight loss. Up to 1 hour of moderate exercise per day is associated with long-term weight maintenance in individuals who have successfully lost weight.

The American College of Sports Medicine recommends 150 minutes of moderate-intensity aerobic physical activity (such as tennis or brisk walking) per week, 75 minutes of vigorous-intensity aerobic exercise (such as jogging or swimming laps) per week, or an equivalent combination of moderate- and vigorous-intensity aerobic activity. Exercise should be spread throughout the week. Weight resistance is also recommended at least twice per week. Exercise physiologists and physical therapists can provide additional support for patients.

Medications can have unpredictable and variable effects on patients' weight, so it is important to review patients' medication regimens and balance their benefits against the probability of weight gain. Multiple medications are associated with weight gain, including corticosteroids, contraceptives and other hormonal agents, and certain antidiabetic, antihypertensive, antidepressant, antipsychotic, antiepileptic, and antihistamine agents. Table 29-1 provides an overview of weight-gaining medications as well as potential

alternatives. When possible, clinicians should prescribe weight-neutral or weight loss-promoting medications. If there are no alternatives, weight gain can be prevented or lessened by selecting the lowest clinically effective dose.

Weight loss achieved by lifestyle modifications alone is often limited and difficult to maintain. Reduced calorie intake and increased energy expenditure are counteracted by adaptive physiologic responses. Appetite increases and resting metabolic rate decreases out of proportion to what would be expected based on changes in body composition. As a result, patients may require antiobesity medications, bariatric surgery, devices, or endoscopic bariatric therapies to achieve and maintain significant weight loss.

Antiobesity medications (Table 29-2) can be considered in patients with a BMI 30 kg/m² or higher or a BMI 27 kg/m² or higher with weight-related comorbidities. Many affect mechanisms regulating appetite through serotonergic, dopaminergic, or noradrenergic pathways. Medications approved for weight management should be viewed as additions to diet and exercise for patients who have been unsuccessful with lifestyle changes alone. The five most widely prescribed antiobesity medications approved by the FDA are phentermine, orlistat, phentermine/topiramate extended release (ER), naltrexone sustained-release (SR)/bupropion SR, and liraglutide. Table 29-2 provides an overview of these medications. In addition to producing weight loss, each medication improves biomarkers including blood sugar, blood pressure, and lipids. The three agents approved since 2012 have stopping rules, which provide weight loss thresholds after 12–16 weeks of treatment under which medication discontinuation is suggested.

Phentermine is the most commonly prescribed adrenergic agonist and antiobesity medication in the United States. In a 28-week controlled trial, participants taking phentermine 15 mg daily lost an average of 6.0 kg compared with 1.5 kg among those assigned to placebo. The maximum recommended dosage of phentermine is 37.5 mg daily, but the dosage should be individualized to the lowest effective dose.

Orlistat works in the gastrointestinal tract to inhibit intestinal lipase, thus reducing dietary fat absorption. It may thereby cause steatorrhea, fecal urgency, abdominal discomfort, and reduced absorption of fat-soluble vitamins. Orlistat is associated with a 9.6% weight loss after 1 year compared to 5.6% with placebo. The recommended dose is 120 mg (Xenical, prescription-strength) or 60 mg (Alli, over-the-counter) three times per day with each main meal containing fat.

The combination of **phentermine** and **topiramate ER** (3.75 mg/23 mg orally daily for 14 days, then 7.5 mg/46 mg orally daily, to a maximum dosage of 15 mg/92 mg orally daily) targets two different weight-regulation mechanisms simultaneously. In a 56-week clinical trial, participants taking 15/92 mg lost significantly more weight (9.8%) than those assigned to 7.5/46 mg (7.8%) or placebo (1.2%). There may be a potential increased risk of orofacial clefts in infants exposed to topiramate during the first trimester of pregnancy.

The combination of **naltrexone SR** and **bupropion SR** (8 mg/90 mg, increasing from 1 tablet orally daily by 1 additional daily tablet each week to a maximum of 2 tablets

Table 29–1. Medications and their effects on weight.

Drug Class	Result: Weight Gain	Result: Weight Neutral (or Minor Weight Gain)	Result: Weight Loss
Antidiabetics	Insulin Meglitinides Sulfonylureas Thiazolidinediones	Alpha-glucosidase inhibitors Bromocriptine Colesevelam DPP-4 inhibitors	GLP-1 agonists Metformin Pramlintide SGLT2 inhibitors
Antihypertensives	Alpha-adrenergic blockers Beta-adrenergic blockers (atenolol, metoprolol, nadolol, propranolol)	ACE inhibitors ARBs Beta-adrenergic blockers (carvedilol, nebivolol) Calcium channel blockers Thiazides	
Antidepressants	Lithium MAOIs Mirtazapine SNRIs (duloxetine, venlafaxine) SSRIs (citalopram, paroxetine) Tricyclic antidepressants (amitriptyline, desipramine, doxepin, imipramine, nortriptyline)	SSRIs (fluoxetine, sertraline)	Bupropion
Antipsychotics	Clozapine Haloperidol Olanzapine Quetiapine Risperidone	Lurasidone Ziprasidone	
Antiepileptics	Carbamazepine Gabapentin Pregabalin Valproic acid	Lamotrigine Levetiracetam Phenytoin	Topiramate Zonisamide
Contraceptives	Medroxyprogesterone acetate	Barrier methods IUDs Surgical sterilization	
Antihistamines	First-generation antihistamines	Second- and third-generation antihistamines	
Steroids	Glucocorticoids	Inhaled steroids Topical steroids	

ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; IUD, intrauterine device; MAOI, monoamine oxidase inhibitor; NSAIDs, nonsteroidal anti-inflammatory drugs; SGLT2, sodium-glucose co-transporter 2; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Adapted, with permission, from Igel LI et al. Practical use of pharmacotherapy for obesity. *Gastroenterology*. 2017 May;152(7):1765–79. Copyright © 2017 AGA Institute. Published by Elsevier, Inc.

twice daily) reduces both appetite and food cravings by targeting two areas of the brain: the arcuate nucleus of the hypothalamus and the mesolimbic dopamine reward circuit. Naltrexone 32 mg/bupropion 360 mg is associated with a 6.1% reduction in body weight compared to 1.3% with placebo after 56 weeks. As with all antidepressants, bupropion carries a black box warning related to a potential increase in suicidality among patients under age 24 during the early phase of treatment.

Liraglutide and **semaglutide** are two glucagon-like peptide-1 (GLP-1) receptor agonists approved by the FDA for the treatment of obesity. **Liraglutide** is initiated at a dose of 0.6 mg subcutaneously daily, increasing by 0.6 mg each week to a maximum of 3.0 mg subcutaneously daily. Liraglutide was initially FDA approved in 2010 for the treatment of type 2 diabetes at doses up to 1.8 mg subcutaneously daily. Liraglutide 3.0 mg is associated with 8.0% weight loss compared to 2.6% with placebo after 56 weeks. Liraglutide

1.8 mg subcutaneously daily has been FDA approved for cardiovascular risk reduction in patients with type 2 diabetes at elevated cardiovascular risk. **Semaglutide**, approved by the FDA in 2021, is given at a dose of 2.4 mg subcutaneously once weekly for chronic weight management in patients with obesity (BMI of 30 kg/m² or greater) or overweight (BMI 27 kg/m² or greater) with a weight-related comorbid condition (eg, hypertension, hypercholesterolemia, or type 2 diabetes). In clinical trials, semaglutide was associated with 14.9% weight loss compared to 2.4% weight loss with placebo after 68 weeks. There is a boxed warning that both liraglutide and semaglutide may cause thyroid C-cell tumors (including medullary thyroid carcinoma) in rodents. It has not been determined if GLP-1 receptor agonists are associated with thyroid C-cell tumors in humans.

Bariatric surgery is the most effective treatment for obesity. It is associated with significant and sustained

Table 29–2. Medications tested in clinical trials for treatment of obesity.

Medication	Mechanism, Dosage, and Available Formulations	Trial and Duration	Trial Arms	Weight Loss (%)	Most Common Adverse Events	Good Candidates	Poor Candidates
Phentermine (Adipex, ¹ Lomaira ²) Schedule IV controlled substance NOTE: approved for short-term use (up to 3 months)	Adrenergic agonist 8–37.5 mg daily (8 mg dose can be prescribed up to three times daily) Capsule, tablet	Aronne LJ et al. ³ 28 weeks	15 mg daily 7.5 mg daily Placebo (topiramate ER and phentermine/topiramate ER arms excluded)	6.06* 5.45* 1.71	Dry mouth, insomnia, dizziness, irritability	Younger patients who need assistance with appetite suppression	Patients with uncontrolled hypertension, active or unstable coronary disease, hyperthyroidism, glaucoma, anxiety, insomnia, or general sensitivity to stimulants Patients with a history of drug abuse or recent MAOI use Patients who are pregnant
Orlistat (Alli, ⁴ Xenical ⁵)	Lipase inhibitor 60–120 mg three times daily with meals Capsule	XENDOS ⁶ 208 weeks	120 mg three times daily Placebo	9.6 (week 52)* 5.25 (week 208)* 5.61 (week 52) 2.71 (week 208)	Fecal urgency, oily stool, flatus with discharge, fecal incontinence	Patients with hypercholesterolemia and/or constipation who can limit their intake of dietary fat	Patients with malabsorption syndromes or other GI conditions that predispose to GI upset/diarrhea Patients who cannot modify the fat content of their diets Patients who are pregnant
Phentermine/ Topiramate Extended Release (Qsymia) ⁷ Schedule IV controlled substance	Adrenergic agonist/neurostabilizer 3.75/23–15/92 mg daily (dose titration) Capsule	EQUIP ⁸ 56 weeks CONQUER ⁹ 56 weeks SEQUEL ¹⁰ 108 weeks (52-week extension of CONQUER trial)	15/92 mg daily 3.75/23 mg daily Placebo 15/92 mg daily 7.5/46 mg daily Placebo 15/92 mg daily 7.5/46 mg daily Placebo	10.9* 5.1* 1.6 9.8* 7.8* 1.2 (weeks 0–56) 10.5* 9.3* 1.8 (weeks 0–108)	Paresthesias, dizziness, dysgeusia, insomnia, constipation, dry mouth	Younger patients who need assistance with appetite suppression	Patients with uncontrolled hypertension, active or unstable coronary disease, hyperthyroidism, glaucoma, anxiety, insomnia, or general sensitivity to stimulants Patients with a history of drug abuse or recent MAOI use Patients with a history of nephrolithiasis Patients who are pregnant or trying to conceive

(continued)

Table 29–2. Medications tested in clinical trials for treatment of obesity. (continued)

Medication	Mechanism, Dosage, and Available Formulations	Trial and Duration	Trial Arms	Weight Loss (%)	Most Common Adverse Events	Good Candidates	Poor Candidates
Naltrexone/ Bupropion Sustained Release (Contrave) ¹¹	Opioid receptor antagonist/ dopamine and norepinephrine reuptake inhibitor 8/90 mg daily to 16/180 mg twice daily Tablet	COR-I ¹² 56 weeks	16/180 mg twice daily	6.1*	Nausea, vomiting, constipation, headache, dizziness, insomnia, dry mouth	Patients who describe cravings for food and/or addictive behaviors related to food; patients who are trying to quit smoking, reduce alcohol intake, and/or who have concomitant depression	Patients with uncontrolled hypertension, uncontrolled pain, recent MAOI use, history of seizures, or any condition that predisposes to seizure, such as anorexia/bulimia nervosa, abrupt discontinuation of alcohol, benzodiazepines, barbiturates, or antiepileptic drugs Patients who are pregnant
			8/180 mg twice daily	5.0*			
			Placebo	1.3			
		COR-II ¹³ 56 weeks	16/180 mg twice daily	6.4*			
			Placebo	1.2			
		COR-BMOD ¹⁴ 56 weeks	16/180 mg twice daily	9.3*			
			Placebo	5.1			
		COR-DIABETES ¹⁵ 56 weeks	16/180 mg twice daily	5.0*			
			Placebo	1.8			
Liraglutide (Saxenda) ¹⁶	GLP-1 receptor agonist 0.6–3.0 mg daily Prefilled pen for subcutaneous injection	SCALE Obesity and Prediabetes ¹⁷ 56 weeks	3.0 mg daily	8.0*	Nausea, vomiting, diarrhea, constipation, dyspepsia, abdominal pain	Patients who report inadequate meal satiety, and/or have type 2 diabetes, prediabetes, or impaired glucose tolerance Patients requiring use of concomitant psychiatric medications	Patients with a history of pancreatitis, personal/family history of MTC or MEN2 Patients with an aversion to needles Patients who are pregnant
		Placebo		2.6			
		SCALE Diabetes ¹⁸ 56 weeks	3.0 mg daily	6*			
		SCALE Maintenance ¹⁹ 56 weeks (after initial $\geq 5\%$ weight loss with low-calorie diet)	1.8 mg daily	4.7*			
		Placebo		2.0			
		3.0 mg daily		6.2*			
		Placebo		0.2			

* $P < 0.001$ vs. placebo.

¹Adipex [package insert]. Tulsa, OK: Physicians Total Care, Inc; 2012.

²Lomaira [package insert]. Newtown, PA: KVK-TECH, INC; 2016.

³Aronne LJ et al. Evaluation of phentermine and topiramate versus phentermine/topiramate extended-release in obese adults. *Obesity (Silver Spring)*. 2013;21:2163.

⁴Alli [package insert]. Moon Township, PA: GlaxoSmithKline Consumer Healthcare, LP; 2015.

⁵Xenical [package insert]. South San Francisco, CA: Genentech USA, Inc; 2015.

⁶Torgerson JS et al. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care*. 2004;27:155.

⁷Qsymia [package insert]. Mountain View, CA: VIVUS, Inc; 2012.

⁸Allison DB et al. Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP). *Obesity (Silver Spring)*. 2012;20:330.

⁹Gadde KM et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. *Lancet*. 2011;377:1341.

¹⁰Garvey WT et al. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study. *Am J Clin Nutr*. 2012;95:297.

¹¹Contrave [package insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc; 2014.

¹²Greenway FL et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2010;376:595.

¹³Apovian CM et al. A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). *Obesity (Silver Spring)*. 2013;21:935.

¹⁴Wadden TA et al. Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial. *Obesity (Silver Spring)*. 2011;19:110.

¹⁵Hollander P et al. Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight and glycemic parameters in overweight and obese patients with type 2 diabetes. *Diabetes Care*. 2013;36:4022.

¹⁶Saxenda [package insert]. Plainsboro, NJ: Novo Nordisk; 2014.

¹⁷Pi-Sunyer X et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *N Engl J Med*. 2015;373:11.

¹⁸Davies MJ et al. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE Diabetes randomized clinical trial. *JAMA*. 2015;314:687.

¹⁹Wadden TA et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet induced weight loss: the SCALE Maintenance randomized study. *Int J Obes (Lond)*. 2013;37:1443. GI, gastrointestinal; GLP-1, glucagon-like peptide-1; MAOI, monoamine oxidase inhibitor; MEN2, multiple endocrine neoplasia syndrome type 2; MTC, medullary thyroid carcinoma; XR, extended release.

Adapted, with permission, from Saunders KH et al. *Obesity pharmacotherapy*. *Med Clin North Am*. 2018;102:135. Copyright © Elsevier, Inc.

weight loss, reduced obesity-related comorbidities, and improved quality of life. Bariatric surgery is associated with lower incidence of cardiovascular events, decreased number of cardiovascular deaths, and reduced overall mortality compared to usual care. The three most common bariatric procedures in the United States are the sleeve gastrectomy, the Roux-en-Y gastric bypass, and the laparoscopic adjustable gastric band. Bariatric surgery can be considered in patients with a BMI 40 kg/m^2 or higher or with a BMI 35 kg/m^2 or higher plus one or more obesity-related complications who are motivated but failed to achieve sufficient weight loss following lifestyle modification, with or without pharmacotherapy. Long-term medical follow-up, lifestyle changes, and adherence to a vitamin regimen are crucial to the success of bariatric surgery. Some patients have difficulty maintaining weight loss and regain some portion of the lost weight. Despite the known benefits of bariatric surgery, less than 1% of eligible patients undergo a weight-loss surgery. This is likely due to limited patient knowledge of the health benefits of surgery, limited provider comfort in recommending surgery, and inadequate insurance coverage.

Sleeve gastrectomy involves removing approximately 70% of the stomach body and antrum along the greater curvature. The fundus of the stomach, which secretes ghrelin, a hormone that stimulates appetite, also is removed. Sleeve gastrectomy is associated with approximately 25% total body weight loss after 1 year. Because this procedure is mainly restrictive (versus the Roux-en-Y gastric bypass, which is also malabsorptive), there is a lower risk of nutritional deficiencies. In general, sleeve gastrectomy is associated with fewer complications than both the Roux-en-Y gastric bypass and laparoscopic adjustable gastric band. Early adverse events include bleeding, leakage along the staple line, stenosis, and vomiting. Late complications include gastroesophageal reflux, nutritional deficiencies, and stomach expansion, leading to decreased restriction. Unlike the other two procedures, sleeve gastrectomy is not reversible.

The **Roux-en-Y gastric bypass** involves a staple partition across the proximal stomach with attachment of a small proximal stomach to a jejunal limb, thus bypassing the remainder of the stomach, duodenum, and the proximal jejunum. Roux-en-Y gastric bypass is associated with approximately 30% total body weight loss at 1 year and greater improvements in comorbid disease markers compared to the two other procedures. Roux-en-Y gastric bypass is associated with a lower rate of gastroesophageal reflux than sleeve gastrectomy and can even alleviate gastroesophageal reflux in patients who have it. It is often recommended over sleeve gastrectomy for patients with type 2 diabetes because it leads to greater long-term remission. Early adverse events associated with Roux-en-Y gastric bypass include obstruction, stricture, leak, and failure of the staple partition of the upper stomach. Late adverse events include nutritional deficiencies (eg, vitamins B₁, B₁₂, D, and iron) and anastomosis ulceration. Dumping syndrome can develop at any time. Roux-en-Y gastric bypass is technically a reversible procedure; however, it is generally only reversed in extreme circumstances.

The **laparoscopic adjustable gastric band** is an inflatable device that is placed around the fundus of the stomach

to create a small pouch. This procedure is associated with 15–20% total body weight loss at 1 year. Laparoscopic adjustable gastric band is reversible and less invasive than the other two procedures, but it is associated with more complications and less weight loss than sleeve gastrectomy and Roux-en-Y gastric bypass. As a result, the band only accounts for 1% of bariatric procedures performed in the United States, and many bands are ultimately removed due to complications. The most common adverse events include nausea, vomiting, obstruction, band erosion or migration, and esophageal dysmotility leading to acid reflux.

Patients who cannot achieve clinically meaningful weight loss with antiobesity medications and who do not undergo bariatric surgery fall into a “treatment gap.” Several **devices and endoscopic procedures** are available that are reversible, minimally invasive, and potentially more effective than antiobesity medications. In addition, they may be less expensive and safer than bariatric surgery for poor surgical candidates. The five FDA-approved devices include two intragastric balloons (Orbera and Obalon), the AspireAssist aspiration device, superabsorbent hydrogel capsules (Plenity), and the TransPyloric Shuttle device. The endoscopic sleeve gastroplasty is a newer option that has gained popularity. It uses an endoscopic suturing device to reduce the cavity of the stomach, mimicking the surgical sleeve gastrectomy without the need for surgical resection.

► When to Refer

- Patients with a BMI greater than or equal to 30 kg/m^2 or a BMI greater than or equal to 27 kg/m^2 with weight-related comorbidities may be referred to an obesity medicine specialist.
- Patients with a BMI greater than or equal to 40 kg/m^2 (or greater than or equal to 35 kg/m^2 with obesity-related morbidities) who have not achieved sufficient weight loss to address health goals following behavioral treatment, with or without pharmacotherapy, may be referred to a bariatric surgeon.

Carlsson LMS et al. Life expectancy after bariatric surgery in the Swedish Obese Subjects study. *N Engl J Med*. 2020;383:1535. [PMID: 33053284]

Hedjoudje A et al. Efficacy and safety of endoscopic sleeve gastroplasty: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2020;18:1043. [PMID: 31442601]

LeBlanc EL et al. Behavioral and pharmacotherapy weight loss interventions to prevent obesity-related morbidity and mortality in adults. Updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2018;320:1172. [PMID: 30326501]

Reges O et al. Association of bariatric surgery using laparoscopic banding, Roux-en-Y gastric bypass, or laparoscopic sleeve gastrectomy vs usual care obesity management with all-cause mortality. *JAMA*. 2018;319:279. [PMID: 29340677]

Tchang BG et al. Best practices in the management of overweight and obesity. *Med Clin North Am*. 2021;105:149. [PMID: 33246516]

US Preventive Services Task Force. Behavioral weight loss interventions to prevent obesity-related morbidity and mortality in adults. US Preventive Services Task Force Recommendation Statement. *JAMA*. 2018;320:1163. [PMID: 30326502]

EATING DISORDERS

ANOREXIA NERVOSA



ESSENTIALS OF DIAGNOSIS

- ▶ Restriction of calorie intake leading to underweight BMI ($BMI < 18.5 \text{ kg/m}^2$).
- ▶ Intense fear of gaining weight or behavior that prevents weight gain.
- ▶ Distorted perception of body image, with undue influence of weight on self-worth.
- ▶ Denial of the medical seriousness of underweight status.

General Considerations

Anorexia nervosa is characterized by underweight BMI, intense fear of gaining weight, and distorted perception of body image. Anorexia nervosa typically begins in the years between adolescence and young adulthood. Ninety percent of patients are female, most of middle and upper socioeconomic status.

The prevalence of anorexia nervosa is greater than previously suggested since prior diagnostic criteria were more restrictive and individuals with anorexia often conceal their illness. Many adolescents have mild versions of the disorder without severe weight loss. The American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5) classifies the severity of anorexia according to BMI: mild, $BMI 17\text{--}18.49 \text{ kg/m}^2$; moderate, $BMI 16\text{--}16.99 \text{ kg/m}^2$; severe, $BMI 15\text{--}15.99 \text{ kg/m}^2$; extreme, $BMI < 15 \text{ kg/m}^2$.

There are two subtypes of anorexia nervosa: binge-eating/purging type and restricting type. The binge-eating/purging subtype is characterized by recurrent episodes of binge-eating or purging (ie, self-induced vomiting and/or abuse of diuretics, laxatives, enemas, cathartics). The restricting subtype is characterized by dieting, fasting, or excessive exercising without associated binge-eating or purging.

The cause of anorexia nervosa is not known. Although multiple endocrinologic abnormalities exist in patients with anorexia nervosa, most authorities believe they are secondary to malnutrition and not the primary disorder. Most experts favor a primary psychiatric origin, but no hypothesis explains all cases. The patient characteristically comes from a family whose members are highly goal-oriented. Patients are often perfectionistic in behavior and exhibit obsessional personality characteristics. Obsessional preoccupation with food is also common.

Clinical Findings

A. Symptoms and Signs

Patients with anorexia nervosa may exhibit severe emaciation and frequently complain of cold intolerance or

constipation. Bradycardia, hypotension, and hypothermia may be present in severe cases. Examination demonstrates loss of body fat, dry and scaly skin, and increased lanugo body hair. Parotid enlargement and edema may also occur. In females of reproductive age, cessation of menstruation is common.

B. Laboratory Findings

Laboratory findings are variable but may include anemia, leukopenia, electrolyte abnormalities, and elevations of blood urea nitrogen (BUN) and serum creatinine. Serum cholesterol levels are often increased. Endocrine abnormalities include depressed levels of luteinizing and follicle-stimulating hormones and impaired response of luteinizing hormone to gonadotropin-releasing hormone.

Diagnosis & Differential Diagnosis

The diagnosis is based on weight loss to a BMI less than 18.5 kg/m^2 , distorted body image, and fear of weight gain or of loss of control over food intake. Other medical or psychiatric illnesses that can account for anorexia and weight loss must be excluded.

Behavioral features required for the diagnosis include intense fear of gaining weight, disturbance of body image, and refusal to exceed a minimal normal weight.

The differential diagnosis includes bulimia nervosa, binge-eating disorder, endocrine and metabolic disorders (eg, panhypopituitarism, Addison disease, hyperthyroidism, and diabetes mellitus), gastrointestinal disorders (eg, Crohn disease and gluten enteropathy), chronic infections (eg, tuberculosis), cancers (eg, lymphoma), and rare central nervous system disorders (eg, hypothalamic tumor).

Treatment

The goal of treatment is restoration of normal body weight and improvement in psychological comorbidities. Hospitalization may be necessary. Treatment programs conducted by experienced teams successfully restore normal weight in approximately two-thirds of cases. The remainder continue to experience difficulties with underweight, eating behaviors, and associated psychiatric conditions. Two percent to 6% of patients die of the complications of the disorder or commit suicide.

Various treatment methods have been used without clear evidence of superiority of one over another. Supportive care by clinicians and family is the most important feature of any therapy. Cognitive-behavioral therapy, intensive psychotherapy, and family therapy may be tried. A variety of medications including tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and lithium carbonate are effective in some cases; however, clinical trial results have been disappointing. Patients with severe malnutrition must be hemodynamically stabilized and may require enteral or parenteral feeding. Forced feedings should be reserved for life-threatening situations, since the goal of treatment is to reestablish normal eating behavior.

► When to Refer

- Adolescents and young adults with otherwise unexplained profound weight loss should be evaluated by a psychiatrist or eating disorders specialist.
- All patients with diagnosed anorexia nervosa should be co-managed with a psychiatrist or eating disorders specialist.

► When to Admit

- Signs of hypovolemia, major electrolyte disorders, and severe protein-energy malnutrition.
- Failure to improve with outpatient management.

Crow SJ. Pharmacologic treatment of eating disorders. *Psychiatr Clin North Am.* 2019;42:253. [PMID: 31046927]

Lock J. Updates on treatments for adolescent anorexia nervosa. *Child Adolesc Psychiatr Clin N Am.* 2019;28:523. [PMID: 31443871]

Resmark G et al. Treatment of anorexia nervosa—new evidence-based guidelines. *J Clin Med.* 2019;8:E153. [PMID: 30700054]
van den Berg E et al. Meta-analysis on the efficacy of psychological treatments for anorexia nervosa. *Eur Eat Disord Rev.* 2019;27:331. [PMID: 31124215]

BULIMIA NERVOSA



ESSENTIALS OF DIAGNOSIS

- ▶ Uncontrolled episodes of binge eating at least once weekly for 3 months.
- ▶ Recurrent inappropriate compensatory behavior to prevent weight gain such as self-induced vomiting, laxatives, diuretics, fasting, or excessive exercise.
- ▶ Excessive concern with body weight and body shape, with undue influence of weight on self-worth.

► General Considerations

Bulimia nervosa is the episodic uncontrolled ingestion of large quantities of food followed by recurrent inappropriate compensatory behavior to prevent weight gain, such as self-induced vomiting, diuretic or cathartic use, strict dieting, or vigorous exercise.

Like anorexia nervosa, bulimia nervosa is predominantly a disorder of young, White, middle- and upper-class women. It is more difficult to detect than anorexia, and some studies have estimated that the prevalence may be as high as 19% in college-aged women.

► Clinical Findings

Patients with bulimia nervosa typically consume large quantities of easily ingested high-calorie foods, usually in secrecy. Some patients may have several such episodes per day over multiple days; others report regular and persistent patterns of binge eating. Binging is usually followed by

vomiting, cathartics, or diuretics and accompanied by feelings of guilt or depression. Periods of binging may be followed by intervals of self-imposed starvation. Body weight may fluctuate but generally is within 20% of normal BMI.

Family and psychological conditions are generally similar to those of patients with anorexia nervosa. Patients with bulimia, however, have a higher incidence of obesity, greater use of cathartics and diuretics, and more impulsive or anti-social behavior. Menstruation is typically preserved.

Medical complications are numerous. Gastric dilatation and pancreatitis have been reported after binges. Vomiting can result in poor dentition, pharyngitis, esophagitis, aspiration, and electrolyte abnormalities. Cathartic and diuretic abuse can also cause electrolyte abnormalities or dehydration. Constipation is common.

► Treatment

Treatment of bulimia nervosa requires supportive care and psychotherapy. Individual, group, family, and behavioral therapy have all been utilized. Antidepressant medications may be helpful. The best results have been with fluoxetine and other SSRIs. Although death from bulimia is rare, the long-term psychiatric prognosis in severe bulimia is worse than that in anorexia nervosa.

► When to Refer

All patients with diagnosed bulimia should be co-managed with a psychiatrist or eating disorders specialist.

Gibson D et al. Medical complications of anorexia nervosa and bulimia nervosa. *Psychiatr Clin North Am.* 2019;42:263. [PMID: 31046928]

Gorrell S et al. Update on treatments for adolescent bulimia nervosa. *Child Adolesc Psychiatr Clin N Am.* 2019;28:537. [PMID: 31443872]

Treasure J et al. Eating disorders. *Lancet.* 2020;395:899. [PMID: 32171414]

DISORDERS OF VITAMIN METABOLISM

THIAMINE (B₁) DEFICIENCY



ESSENTIALS OF DIAGNOSIS

- ▶ Most common in patients with chronic alcohol use disorder (alcoholism).
- ▶ Early symptoms include anorexia, muscle cramps, paresthesias, and irritability.
- ▶ Advanced syndromes include high-output heart failure ("wet beriberi"), peripheral nerve disorders, and Wernicke-Korsakoff syndrome ("dry beriberi").

► General Considerations

Most thiamine deficiency in the United States is due to chronic alcohol use disorder, with poor dietary intake of

thiamine and impaired thiamine absorption, metabolism, and storage. It is also associated with malabsorption (eg, following bariatric surgery), dialysis, and other causes of chronic protein–calorie undernutrition. Thiamine depletion can be precipitated when patients with low thiamine are given a large carbohydrate load, such as an intravenous dextrose infusion.

► Clinical Findings

Early manifestations of thiamine deficiency include anorexia, muscle cramps, paresthesias, and irritability. Advanced deficiency primarily affects the cardiovascular system (“wet beriberi”) or the nervous system (“dry beriberi”). Wet beriberi occurs in thiamine deficiency accompanied by severe physical exertion and high carbohydrate intake. Dry beriberi occurs in thiamine deficiency accompanied by inactivity and low calorie intake.

Wet beriberi is characterized by marked peripheral vasodilation resulting in high-output heart failure with dyspnea, tachycardia, cardiomegaly, pulmonary edema, and peripheral edema with warm extremities mimicking cellulitis.

Dry beriberi involves both the peripheral and the central nervous systems. Peripheral nerve involvement is typically a symmetric motor and sensory neuropathy with pain, paresthesias, and loss of reflexes. Legs are affected more than arms. Central nervous system involvement results in Wernicke–Korsakoff syndrome. Wernicke encephalopathy consists of nystagmus progressing to ophthalmoplegia, truncal ataxia, and confusion. Korsakoff syndrome includes amnesia, confabulation, and impaired learning.

► Diagnosis

In most instances, the clinical response to empiric thiamine therapy is used to support a diagnosis of thiamine deficiency. The most commonly used biochemical tests measure thiamine concentration directly, while other assays measure erythrocyte transketolase activity and urinary thiamine excretion. Normal thiamine values typically range from 70 nmol/L to 180 nmol/L.

► Treatment

Thiamine deficiency is treated with large parenteral doses of thiamine. Fifty to 100 mg/day is initially administered intravenously, followed by daily oral doses of 5–10 mg/day. All patients should simultaneously receive therapeutic doses of other water-soluble vitamins. Treatment results in complete resolution in one-fourth immediately and another one-fourth over days, but half obtain only partial or no benefit.

► When to Refer

Patients with signs of dry beriberi or Wernicke–Korsakoff syndrome should be referred to a neurologist. Patients with signs of wet beriberi should be referred to a cardiologist.

THIAMINE TOXICITY

There is no known toxicity of thiamine.

- Chandrakumar A et al. Review of thiamine deficiency disorders: Wernicke encephalopathy and Korsakoff psychosis. *J Basic Clin Physiol Pharmacol.* 2018;30:153. [PMID: 30281514]
- Dhir S et al. Neurological, psychiatric, and biochemical aspects of thiamine deficiency in children and adults. *Front Psychiatry.* 2019;10:207. [PMID: 31019473]
- DiNicolantonio JJ et al. Thiamine and cardiovascular disease: a literature review. *Prog Cardiovasc Dis.* 2018;61:27. [PMID: 29360523]

RIBOFLAVIN (B₂) DEFICIENCY

► Clinical Findings

Riboflavin deficiency usually occurs in combination with other vitamin deficiencies. Dietary inadequacy, interactions with medications, alcohol use disorder, and other causes of protein–calorie undernutrition are the most common causes.

Manifestations of riboflavin deficiency include cheilosis, angular stomatitis, glossitis, seborrheic dermatitis, weakness, corneal vascularization, and anemia.

► Diagnosis

Riboflavin deficiency can be confirmed by measuring the riboflavin-dependent enzyme erythrocyte glutathione reductase. Urinary riboflavin excretion and serum levels of plasma and red cell flavins can also be measured.

► Treatment

When suspected, riboflavin deficiency is usually treated empirically with foods such as meat, fish, and dairy products or with oral preparations of the vitamin. Administration of 5–15 mg/day until clinical findings resolve is usually adequate. Riboflavin can also be given parenterally.

RIBOFLAVIN TOXICITY

There is no known toxicity of riboflavin.

- Saeedisomeolia A et al. Riboflavin in human health: a review of current evidences. *Adv Food Nutr Res.* 2018;83:57. [PMID: 29477226]

NIACIN DEFICIENCY

► General Considerations

“Niacin” is a generic term for nicotinic acid and other derivatives with similar nutritional activity. Unlike most other vitamins, niacin can be synthesized from the amino acid tryptophan. Niacin is an essential component of the co-enzymes nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), which are involved in many oxidation-reduction reactions. The major food sources of niacin are

proteins containing tryptophan and numerous cereals, vegetables, and dairy products.

Historically, niacin deficiency occurred when corn, which is relatively deficient in both tryptophan and niacin, was the major source of calories. Currently, niacin deficiency is more commonly due to alcoholism and nutrient-drug interactions. Niacin deficiency can also occur in inborn errors of metabolism. Niacin in the form of nicotinic acid is used therapeutically for the treatment of hypercholesterolemia and hypertriglyceridemia. Niacinamide (the form of niacin generally used to treat niacin deficiency) does not exhibit the lipid-lowering effects of nicotinic acid.

► Clinical Findings

As with other B vitamins, early manifestations of niacin deficiency are nonspecific—anorexia, weakness, irritability, mouth soreness, glossitis, stomatitis, and weight loss. More advanced deficiency results in the classic triad of pellagra: dermatitis, diarrhea, and dementia. The dermatitis is symmetric, involving sun-exposed areas. Skin lesions are dark, dry, and scaly. The dementia begins with insomnia, irritability, and apathy and progresses to confusion, memory loss, hallucinations, and psychosis. The diarrhea can be severe and may result in malabsorption due to atrophy of the intestinal villi. Advanced pellagra can result in death.

► Diagnosis

In early deficiency, diagnosis requires a high index of suspicion. Low levels may be found in patients with generalized undernutrition. In advanced cases, the diagnosis of pellagra can be made on clinical grounds. Niacin can be measured in serum or plasma.

► Treatment

Niacin deficiency can be effectively treated with oral niacin, usually given as nicotinamide (10–150 mg/day).

NIACIN TOXICITY

At the high doses of niacin used to treat hyperlipidemia, side effects are common. These include cutaneous flushing (partially prevented by pretreatment with aspirin, 81–325 mg/day, and use of extended-release preparations) and gastric irritation. Elevation of liver enzymes, hyperglycemia, and gout are less common untoward effects.

D'Andrea E et al. Assessment of the role of niacin in managing cardiovascular disease outcomes: a systematic review and meta-analysis. *JAMA Netw Open*. 2019;2:e192224. [PMID: 30977858]

VITAMIN B₆ DEFICIENCY

Vitamin B₆ deficiency most commonly occurs as a result of alcoholism or interactions with medications, especially isoniazid, cycloserine, penicillamine, and oral contraceptives. A number of inborn errors of metabolism and other

pyridoxine-responsive syndromes, particularly pyridoxine-responsive anemia, are not clearly due to vitamin deficiency but commonly respond to high doses of the vitamin. Patients with common variable immunodeficiency may have concomitant vitamin B₆ deficiency.

► Clinical Findings

Vitamin B₆ deficiency results in clinical symptoms similar to those of other B vitamin deficiencies, including mouth soreness, glossitis, cheilosis, weakness, and irritability. Severe deficiency can result in peripheral neuropathy, anemia, and seizures.

► Diagnosis

The diagnosis of vitamin B₆ deficiency can be confirmed by measurement of pyridoxal phosphate in blood.

► Treatment

Vitamin B₆ deficiency can be effectively treated with vitamin B₆ supplements (10–20 mg/day orally). Some patients taking medications that interfere with pyridoxine metabolism (such as isoniazid) may need doses as high as 50–100 mg/day orally to prevent vitamin B₆ deficiency. This is particularly true for patients who are more likely to have diets marginally adequate in vitamin B₆, such as older patients and patients with alcohol use disorder. Inborn errors of metabolism and pyridoxine-responsive syndromes often require doses up to 600 mg/day orally.

VITAMIN B₆ TOXICITY

A sensory neuropathy, at times irreversible, occurs in patients receiving large doses of vitamin B₆ (200–2000 mg/day).

VITAMIN B₁₂ & FOLATE

Vitamin B₁₂ (cobalamin) and folate are discussed in Chapter 13.

VITAMIN C (ASCORBIC ACID) DEFICIENCY

Most cases of vitamin C deficiency seen in the United States are due to dietary inadequacy in older patients and patients with chronic alcohol use disorder. Patients with chronic illnesses such as cancer and chronic kidney disease and individuals who smoke cigarettes are also at risk.

► Clinical Findings

Early manifestations of vitamin C deficiency are nonspecific and include malaise and weakness. In more advanced stages, the typical features of scurvy develop. Manifestations include perifollicular hemorrhages, perifollicular hyperkeratotic papules, petechiae, purpura, splinter hemorrhages, bleeding gums, hemarthroses, and subperiosteal hemorrhages. Anemia is common, and wound healing is impaired. The late stages of scurvy are characterized by edema, oliguria, neuropathy, intracerebral hemorrhage, and death.

► Diagnosis

The diagnosis of advanced scurvy can be made clinically on the basis of skin lesions in the proper clinical situation. Atraumatic hemarthrosis is also highly suggestive. The diagnosis can be confirmed with decreased plasma ascorbic acid levels, typically below 0.2 mg/dL.

► Treatment

Adult scurvy can be treated with ascorbic acid 300–1000 mg/day orally. Improvement generally occurs within days.

VITAMIN C TOXICITY

Very large doses of vitamin C can cause gastric irritation, flatulence, or diarrhea. Oxalate kidney stones are of theoretical concern because ascorbic acid is metabolized to oxalate, but stone formation has not been frequently reported. Vitamin C can also confound common diagnostic tests by causing false-negative results for some fecal occult blood tests and both false-negative and false-positive results for urine glucose.

Granger M et al. Dietary vitamin C in human health. *Adv Food Nutr Res*. 2018;83:281. [PMID: 29477224]

VITAMIN A DEFICIENCY

► Clinical Findings

Vitamin A deficiency is one of the most common vitamin deficiency syndromes, particularly in developing countries. In certain regions, it is the most common cause of blindness. In the United States, it is usually due to fat malabsorption syndromes or mineral oil laxative abuse and occurs most commonly in older adults and patients with malabsorptive conditions.

Night blindness is the earliest symptom. Dryness of the conjunctiva (xerosis) and the development of small white patches on the conjunctiva (Bitot spots) are early signs. Ulceration and necrosis of the cornea (keratomalacia), perforation, endophthalmitis, and blindness are late manifestations. Xerosis and hyperkeratinization of the skin and loss of taste may also occur.

► Diagnosis

Abnormalities of dark adaptation are strongly suggestive of vitamin A deficiency. Serum levels below the normal range of 30–65 mg/dL are commonly seen in advanced deficiency.

► Treatment

Night blindness, poor wound healing, and other signs of early deficiency can be effectively treated with vitamin A 30,000 international units orally daily for 1 week. Advanced deficiency with corneal damage can be treated with 20,000 international units/kg orally for at least 5 days. The potential antioxidant effects of beta-carotene can be achieved

with supplements of 25,000–50,000 international units of beta-carotene.

VITAMIN A TOXICITY

Excess intake of beta-carotene (hypercarotenosis) results in staining of the skin a yellow-orange color but is otherwise benign. Skin changes are most marked on the palms and soles, while scleras remain white, clearly distinguishing hypercarotenosis from jaundice.

Excessive vitamin A (hypervitaminosis A), on the other hand, can be quite toxic. Chronic toxicity usually occurs after ingestion of daily doses of over 50,000 international units/day for more than 3 months. Early manifestations include dry, scaly skin, hair loss, mouth sores, painful hyperostoses, anorexia, and vomiting. More serious findings include hypercalcemia; increased intracranial pressure with papilledema, headaches, and decreased cognition; and hepatomegaly, which can progress to cirrhosis. Acute toxicity can result from ingestion of excessive doses of vitamin A via medications or supplements. Manifestations include nausea, vomiting, abdominal pain, headache, papilledema, and lethargy.

The diagnosis can be confirmed by elevations of serum vitamin A levels. The only treatment is withdrawal of vitamin A from the diet. Most symptoms and signs improve rapidly.

Hombali AS et al. Fortification of staple foods with vitamin A for vitamin A deficiency. *Cochrane Database Syst Rev*. 2019; 5:CD010068. [PMID: 31074495]

VITAMIN D

Vitamin D is discussed in Chapter 26.

VITAMIN E DEFICIENCY

► Clinical Findings

Clinical deficiency of vitamin E is most commonly due to severe malabsorption or abetalipoproteinemia in adults and chronic cholestatic liver disease, biliary atresia, or cystic fibrosis in children. Manifestations of deficiency include areflexia, disturbances of gait, decreased vibration and proprioception, and ophthalmoplegia.

► Diagnosis

Plasma vitamin E levels can be measured; normal levels are 0.5–0.7 mg/dL or higher. Since vitamin E is normally transported in lipoproteins, the serum level should be interpreted in relation to circulating lipid levels.

► Treatment

The optimum therapeutic dose of vitamin E has not been defined. Large doses, often administered parenterally, can be used to improve the neurologic complications seen in abetalipoproteinemia and cholestatic liver disease. Vitamin E supplementation may also provide benefit in patients with nonalcoholic fatty liver disease.

VITAMIN E TOXICITY

Clinical trials have suggested an increase in all-cause mortality with high dose (greater than 400 international units/day) vitamin E supplements. Large doses of vitamin E can also increase the vitamin K requirement and result in bleeding in patients taking oral anticoagulants.

VITAMIN K

Vitamin K is discussed in Chapter 14.

DIET THERAPY

Specific therapeutic diets can complement the medical management of most common illnesses. Dietary modifications can be difficult to sustain, and patients may benefit from the support of a registered dietitian or other provider who can offer guidance. Eliciting a food recall is a helpful strategy to provide insight into a patient's dietary preferences and restrictions and provides information about nutrient content in the current diet. Ongoing food tracking can improve dietary adherence.

Therapeutic diets can be divided into three groups: (1) diets that alter food consistency, (2) diets that restrict or modify dietary components, and (3) diets that supplement dietary components.

DIETS THAT ALTER CONSISTENCY

Clear Liquid Diet

This diet provides adequate water, 500–1000 kcal as simple sugar, and some electrolytes. It is fiber-free and requires minimal digestion or intestinal motility.

A clear liquid diet is useful for patients with resolving postoperative ileus, acute gastroenteritis, partial intestinal obstruction, and in preparation for diagnostic gastrointestinal procedures. It is commonly used as the first diet for patients who have been taking nothing by mouth for a long period. Because of the low calorie and minimal protein content of the clear liquid diet, it is used only for short durations.

Full Liquid Diet

The full liquid diet provides adequate water and can be designed to provide sufficient calories and protein. Vitamins and minerals—especially folic acid, iron, and vitamin B₆—may be inadequate and should be provided in the form of supplements. Dairy products, protein shakes, and soups are used to supplement clear liquids. Commercial oral supplements can also be incorporated into the diet or used alone.

This diet is low in residue and can be used in patients with difficulty chewing or swallowing, with partial obstructions, or in preparation for certain diagnostic procedures. Full liquid diets are commonly used following clear liquid diets in patients who have been taking nothing by mouth for a long period.

Soft Diets

Soft diets are designed for patients unable to chew or swallow hard food. Tender foods are used, and most raw fruits and vegetables, coarse breads, and cereals are eliminated. Soft diets are commonly used to assist in progression from full liquid diets to regular diets in postoperative patients, patients who are too weak or those whose dentition is too poor for a regular diet, head and neck surgical patients, and patients with esophageal strictures. The soft diet can be designed to meet all nutritional requirements.

DIETS THAT RESTRICT NUTRIENTS

Diets can be designed to restrict (or eliminate) virtually any nutrient or food component. The most commonly used restricted diets are those that limit sodium, fat, carbohydrate, and protein. Other restrictive diets include gluten restriction in gluten enteropathy, potassium and phosphate reduction in chronic kidney disease, and elimination of certain allergens for food allergies.

Sodium-Restricted Diets

Low-sodium diets can be useful in the management of hypertension and in conditions in which sodium retention and edema are prominent features, particularly heart failure, chronic liver disease, and chronic kidney disease. Sodium restriction may be beneficial with or without diuretic therapy. When used in conjunction with diuretics, sodium restriction may allow lower dosages of diuretic medications and may prevent side effects. For example, sodium restriction will decrease diuretic-related potassium losses by reducing distal tubule sodium delivery.

Typical American diets contain 4–6 g (175–260 mEq) of sodium per day. A no-added-salt diet contains approximately 3 g (132 mEq) of sodium per day. Further restriction can be achieved with diets of 2 or 1 g of sodium per day. Diets with more severe restriction are difficult to adhere to and are rarely used. National Academies of Sciences, Engineering, and Medicine guidelines recommend 2.3 g of sodium per day (approximately 1 teaspoon of salt).

Dietary sodium includes sodium naturally occurring in foods, sodium added during food processing, and sodium added during cooking and at the table. Approximately 80% of the current US dietary intake is from processed and pre-prepared foods. Diets designed for 2.3 g of sodium per day require elimination of most processed foods, added salt, and foods with particularly high sodium content. Many patients with mild hypertension will achieve significant reductions in blood pressure (approximately 5 mm Hg diastolic) with this degree of sodium restriction.

Diets allowing 1 g of sodium require further restriction of commonly consumed foods. Special “low-sodium” products are available to facilitate such diets. These diets are difficult for most people to follow and are generally reserved for hospitalized patients, most commonly those with heart failure, chronic kidney disease, or severe liver disease and ascites.

► Fat-Restricted Diets & Low-Saturated-Fat Diets

Traditional fat-restricted diets are useful in the treatment of fat malabsorption syndromes. Such diets will improve the symptoms of diarrhea with steatorrhea independent of the primary physiologic abnormality by limiting the quantity of fatty acids that reach the colon. The degree of fat restriction necessary to control symptoms must be individualized. Patients with severe malabsorption can be limited to 40–60 g of fat per day. Diets containing 60–80 g of fat per day can be designed for patients with less severe abnormalities.

Fat-restricted diets that specifically restrict saturated fats are the mainstay of dietary treatment of hyperlipidemia with elevated low-density lipoprotein cholesterol (see Chapter 28). Similar diets are often recommended for the prevention of coronary artery disease (see Chapter 10). The large Women's Health Initiative Dietary Modification Trial, however, did not show significant benefit of a low-fat diet on weight control or prevention of cardiovascular disease or cancer. In contrast, a study of Mediterranean diets, supplemented by nuts or extra-virgin olive oil, demonstrated a reduction in cardiovascular events. Plant-based diets, defined by low frequency of animal food consumption, have been increasingly recommended for their health benefits. Numerous studies have found diets enriched with high-quality plant foods, such as whole grains, fruits, vegetables, and nuts, to be associated with lower risk of cardiovascular end points.

The aim of low-fat diets is to restrict total fat to less than 30% of calories and saturated fat to 7% of calories. More extreme restriction offers little further advantage in modification of serum lipids. Low-fat diets can be augmented with the addition of plant stanols and sterols and with soluble dietary fiber to further reduce serum lipids.

► Carbohydrate-Restricted Diets

Low carbohydrate diets restrict carbohydrate intake to at most 50–100 g/day. Consumption of foods that contain higher protein and fat with lower carbohydrate content has been shown to promote satiety. Carbohydrate-restricted diets, including low glycemic index diets (see Chapter 27), can be particularly helpful for patients with type 2 diabetes and other forms of insulin resistance to reduce both blood sugar and weight. Several studies investigating the efficacy of low-fat versus low-carbohydrate diets for weight loss show no clear benefit of one versus the other.

► Protein-Restricted Diets

Protein-restricted diets are most commonly used in patients with hepatic encephalopathy due to chronic liver disease and in patients with advanced chronic kidney disease to slow the progression of early disease and to decrease symptoms of uremia in more severe disease.

Protein restriction is intended to limit the production of nitrogenous waste products. Energy intake must be adequate to facilitate the efficient use of dietary protein. A sufficient quantity of proteins (at least 0.6 g/kg/day in most

patients) must be provided to meet minimal requirements. Patients with encephalopathy who do not respond to this degree of restriction are unlikely to respond to more severe restriction.

DIETS THAT SUPPLEMENT NUTRIENTS

► High-Fiber Diets

Dietary fiber is a diverse group of plant constituents that is resistant to digestion by the human digestive tract. Guidelines suggest that adult men should eat 30–38 g of fiber per day and adult women 21–25 g/day. Typical US diets, however, contain about half of that amount. Epidemiologic evidence suggests that populations consuming greater quantities of fiber have a lower incidence of certain gastrointestinal disorders, including diverticulitis and, in some studies, colon cancer as well as a lower risk of cardiovascular disease. A meta-analysis of 22 studies suggested that each 7 g of dietary fiber was associated with a 9% decrease in first cardiovascular event.

Diets high in dietary fiber (21–38 g/day) are commonly used in the management of a variety of gastrointestinal disorders such as irritable bowel syndrome and recurrent diverticulitis. Diets high in fiber, particularly soluble fiber, may also be useful to reduce blood sugar in patients with diabetes and to reduce cholesterol levels in patients with hypercholesterolemia. Good sources of soluble fiber are oats, nuts, seeds, legumes, and most fruits. Foods with insoluble fiber include whole wheat, brown rice, other whole grains, and most vegetables. For some patients, the addition of psyllium or natural bran may be a useful adjunct to increase dietary fiber.

► High-Potassium Diets

Potassium-supplemented diets are used most commonly to compensate for potassium losses caused by diuretics. Although potassium losses can be partially prevented by using lower doses of diuretics, concurrent sodium restriction, and potassium-sparing diuretics, some patients require additional potassium to prevent hypokalemia. High-potassium diets may also have a direct antihypertensive effect. Typical American diets contain about 3 g (80 mEq) of potassium per day. High-potassium diets commonly contain 4.5–7 g (120–180 mEq) of potassium per day.

Most fruits, vegetables, and their juices contain high concentrations of potassium. Supplemental potassium can also be provided with potassium-containing salt substitutes or as potassium chloride in solution or capsules, but this is rarely necessary if the above measures are followed to prevent potassium losses and to supplement dietary potassium.

► High-Calcium Diets

Adequate intake of dietary calcium has been recommended for the prevention of postmenopausal osteoporosis, the prevention and treatment of hypertension, and the prevention of colon cancer. The Women's Health Initiative, however, suggested that calcium and vitamin D supplementation did not prevent fractures or colon cancer.

Observational studies have also suggested that calcium supplements, especially when taken without vitamin D, may be associated with an increased risk of coronary heart disease. The recommended dietary allowance for the total calcium intake (from food and supplements) in adults ranges from 1000 mg/day to 1200 mg/day. Average American daily intakes are approximately 700 mg/day.

Dairy products are the primary dietary sources of calcium in the United States. An 8-ounce glass of milk, for example, contains approximately 300 mg of calcium. Patients with lactose intolerance who cannot tolerate liquid dairy products may be able to drink lactose-free milk, take supplemental lactase enzyme supplements, or tolerate nonliquid products such as yogurt and aged cheeses. Leafy green vegetables also contain high concentrations of calcium.

Baden MY et al. Changes in plant-based diet quality and total and cause-specific mortality. *Circulation*. 2019;140:979. [PMID: 31401846]

Estruch R et al; PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. *N Engl J Med*. 2018;378:e34. [PMID: 29897866]

Li Z et al. JAMA patient page. Ketogenic diets. *JAMA*. 2020; 323:386. [PMID: 31990316]

National Academies of Sciences, Engineering, and Medicine 2019. *Dietary Reference Intakes for Sodium and Potassium*. Washington, DC: The National Academies Press. <https://doi.org/10.17226/25353>.

Shan Z et al. Trends in dietary carbohydrate, protein, and fat intake and diet quality among US adults, 1999–2016. *JAMA*. 2019;322:1178. [PMID: 31550032]

NUTRITIONAL SUPPORT

Jonathan A. Waitman, MD

Nutritional support is the provision of nutrients to patients who cannot meet their nutritional requirements by eating standard diets. Nutrients may be delivered enterally (using oral nutritional supplements; nasogastric, nasoduodenal, and nasojejunal feeding tubes; and tube

enterostomies) or parenterally (using lines or catheters placed in peripheral or central veins, respectively). Current nutritional support techniques permit adequate nutrient delivery to most patients. Nutritional support should be utilized, however, only if it is likely to improve the patient's clinical outcome.

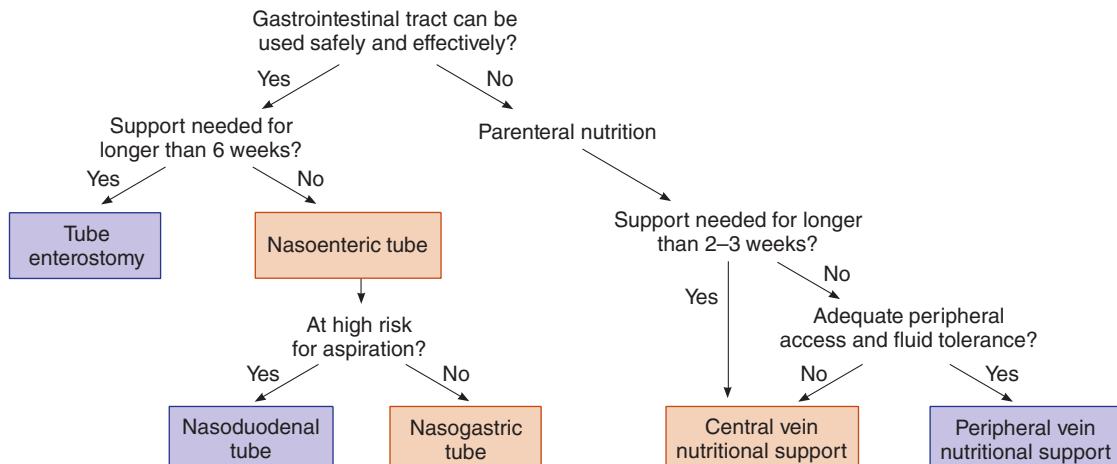
INDICATIONS FOR NUTRITIONAL SUPPORT

The precise indications for nutritional support remain controversial. Most authorities agree that nutritional support is indicated for at least four groups of adult patients: (1) those with inadequate bowel syndromes, (2) those with severe prolonged hypercatabolic states (eg, due to extensive burns, trauma, mechanical ventilation), (3) those requiring prolonged therapeutic bowel rest, and (4) those with severe protein–calorie undernutrition with a treatable disease who have sustained a loss of 10% body weight at 6 months or 20% body weight at 1 year. In most other conditions, it has been difficult to prove the efficacy of nutritional support over treatment without such support.

The American Society for Parenteral and Enteral Nutrition (ASPEN) has published recommendations for the rational use of nutritional support. These emphasize the need in each patient to individualize the decision to begin nutritional support, weighing the risks, benefits, and costs. They also reinforce the need to identify high-risk malnourished patients by nutritional assessment.

Nutritional Support Methods

Selection of the most appropriate nutritional support method involves consideration of gastrointestinal function, the anticipated duration of nutritional support, and the ability of each method to meet the patient's nutritional requirements. The method chosen should meet the nutritional needs with the lowest risk and cost. For most patients, enteral feeding is safer, less expensive, and offers significant physiologic advantages. An algorithm for selection of the most appropriate nutritional support method is presented in Figure 29–1.



▲ Figure 29–1. Nutritional support method decision tree.

Prior to initiating specialized enteral nutritional support, efforts should be made to supplement food intake. Attention to patient food preferences, timing of meals in relation to diagnostic procedures and required medications, and the use of foods brought to the hospital by family and friends can often increase oral intake. Patients unable to eat enough at regular mealtimes to meet nutritional requirements can be given **oral supplements** as snacks or to replace low-calorie beverages. Oral supplements of differing nutritional composition are available for the purpose of individualizing the diet in accordance with specific clinical requirements. Fiber and lactose content, caloric density, protein level, amino acid profiles, vitamin K, and calcium can all be modified as necessary.

Patients requiring nutritional support who are unable to take adequate oral nutrition but have functioning gastrointestinal tracts are candidates for **liquid artificial nutrition (“tube feedings”)**. Small-bore feeding tubes are placed via the nose into the stomach, duodenum, or jejunum. Patients able to sit up in bed who can protect their airways can be fed into the stomach. Because of the increased risk of aspiration, patients who cannot adequately protect their airways should be fed post-pylorically (though this may not prevent all aspirations). Feeding tubes can usually be passed into the duodenum by leaving an extra length of tubing in the stomach and placing the patient in the right decubitus position. Metoclopramide, 10 mg intravenously, can be given 20 minutes prior to insertion and continued every 6 hours thereafter to facilitate passage through the pylorus. Fluoroscopic or endoscopic guidance occasionally is necessary to insert the tube distal to the pylorus. Placement of nasogastric and, particularly, nasoduodenal tubes should be confirmed radiographically before delivery of feeding solutions.

Liquid artificial nutrition can also be accomplished by placing tubes directly into the gastrointestinal tract using **tube enterostomies**. Most tube enterostomies are placed in patients who require long-term enteral nutritional support. Gastrostomies have the advantage of allowing bolus feedings, while jejunostomies require continuous infusions. Gastrostomies—like nasogastric feeding—should be used only in patients at low risk for aspiration. Tube enterostomies can be placed surgically, by interventional radiology or by endoscopy.

Patients who require nutritional support but whose gastrointestinal tracts are nonfunctional should receive **parenteral nutritional support**. Most patients receive parenteral feedings via a central vein—most commonly the subclavian vein. Peripheral veins can be used in some patients, but this is rarely tolerated for more than a few weeks because of the high osmolality of parenteral solutions.

Peripheral vein nutritional support is most commonly used in patients with nonfunctioning gastrointestinal tracts who require immediate support but whose clinical status is expected to improve within 1–2 weeks, allowing enteral feeding. Peripheral vein nutritional support is administered via standard intravenous lines. Solutions should always include lipid and dextrose in combination with amino acids to provide adequate

nonprotein calories. Serious adverse events are infrequent, but there is a high incidence of phlebitis and infiltration of intravenous lines.

Central vein nutritional support is delivered via intravenous catheters placed percutaneously using aseptic technique. Proper placement in the superior vena cava is documented radiographically before the solution is infused. Catheters must be carefully maintained by experienced nursing personnel and used solely for nutritional support to prevent infection and other catheter-related complications.

NUTRITIONAL REQUIREMENTS

Each patient's nutritional requirements should be determined independently of the method of nutritional support. In most situations, solutions of equal nutrient value can be designed for delivery via enteral and parenteral routes, but differences in absorption must be considered. A complete nutritional support solution must contain water, energy, amino acids, electrolytes, vitamins, minerals, and essential fatty acids.

► Water

For most patients, water requirements can be calculated by allowing 1500 mL for the first 20 kg of body weight plus 20 mL for every kilogram over 20. Additional losses should be replaced as they occur. For patients with a normal BMI, fluid needs are about 30–35 mL/kg, or approximately 1 mL/kcal of energy required.

► Energy

Energy requirements can be estimated by one of three methods: (1) by using standard equations to calculate BEE plus additional calories for activity and illness, (2) by applying a simple calculation based on calories per kilogram of body weight, or (3) by measuring energy expenditure with indirect calorimetry.

BEE can be estimated by the **Harris–Benedict equation**: for men, $BEE = 666 + (13.7 \times \text{weight in kg}) + (5 \times \text{height in cm}) - (6.8 \times \text{age in years})$. For women, $BEE = 655 + (9.5 \times \text{weight in kg}) + (1.8 \times \text{height in cm}) - (4.7 \times \text{age in years})$. For undernourished patients, actual body weight should be used. For patients with obesity, a weight in between ideal body weight and actual body weight can be used: ideal body weight + 0.4(actual body weight – ideal body weight). For most patients, an additional 20–50% of BEE is administered as nonprotein calories to accommodate energy expenditures during activity or relating to illness. Occasional patients are noted to have energy expenditures greater than 150% of BEE.

Energy requirements can also be estimated by multiplying actual body weight in kilograms by 25–30 kcal/kg/day.

Both of these methods provide imprecise estimates of actual energy expenditures, especially for markedly underweight, overweight, and critically ill patients. Studies using indirect calorimetry have demonstrated that as many as 30–40% of patients will have measured expenditures 10% above or below estimated values.

► Protein

Protein and energy requirements are closely related. If adequate calories are provided, most patients can be given 0.8–1.2 g of protein per kilogram per day. Patients under moderate to severe stress should receive up to 1.5 g/kg/day. As in the case of energy requirements, actual weights should be used for normal and underweight patients and ideal body weight + 0.4(actual body weight – ideal body weight) can be used for patients with obesity.

Patients who are receiving protein without adequate calories will catabolize protein for energy rather than utilizing it for protein synthesis. Thus, when energy intake is low, excess protein is needed for nitrogen balance.

► Electrolytes & Minerals

Requirements for sodium, potassium, and chloride vary widely. Most patients require 45–145 mEq/day of each. The actual requirement in individual patients will depend on the patient's cardiovascular, renal, endocrine, and gastrointestinal status as well as measurements of serum concentration.

Patients receiving enteral nutritional support should receive adequate vitamins and minerals according to recommended daily allowances. Most premixed enteral solutions provide sufficient vitamins and minerals as long as adequate calories are administered.

Patients receiving parenteral nutritional support require smaller amounts of minerals: calcium, 10–15 mEq/day; phosphorus, 15–20 mEq per 1000 nonprotein calories; and magnesium, 16–24 mEq/day. Most patients receiving nutritional support do not require supplemental iron because body stores are adequate. Iron nutrition should be monitored closely by following the hemoglobin concentration, mean corpuscular volume, and iron studies.

Patients receiving parenteral nutritional support should be given the trace elements zinc (about 5 mg/day) and copper (about 2 mg/day). Patients with diarrhea will require additional zinc to replace fecal losses. Additional trace elements—especially chromium, manganese, and selenium—are provided to patients receiving long-term parenteral nutrition.

Parenteral vitamins are provided daily. Standardized multivitamin solutions are currently available to provide adequate quantities of vitamins A, B₁₂, C, D, E, thiamine, riboflavin, niacin, pantothenic acid, pyridoxine, folic acid, and biotin. Vitamin K is not given routinely but administered when the prothrombin time becomes abnormal.

► Essential Fatty Acids

Patients receiving nutritional support should be given 2–4% of their total calories as linoleic acid to prevent essential fatty acid deficiency. Most prepared enteral solutions contain adequate linoleic acid. Patients receiving parenteral nutrition should be given at least 250 mL of a 20% intravenous fat (emulsified soybean or safflower oil) two to seven times per week depending on calorie requirements. Intravenous fat can also be used as an energy source in place of dextrose.

ENTERAL NUTRITIONAL SUPPORT SOLUTIONS

Most patients who require enteral nutritional support can be given commercially prepared enteral solutions (Table 29–3). Nutritionally complete solutions have been designed to provide adequate proportions of water, energy, protein, and micronutrients. Nutritionally incomplete solutions are also available to provide specific macronutrients (eg, protein, carbohydrate, and fat) to supplement complete solutions for patients with unusual requirements or to design solutions that are not available commercially.

Nutritionally complete solutions are characterized as follows: (1) by osmolality (isotonic or hypertonic), (2) by lactose content (present or absent), (3) by the molecular form of the protein component (intact proteins, peptides, or amino acids), (4) by the quantity of protein and calories provided, and (5) by fiber content (present or absent). For most patients, isotonic solutions containing no lactose or fiber are preferable. Such solutions generally contain moderate amounts of fat and intact protein. Most commercial isotonic solutions contain 1000 kcal and 37–45 g of protein per liter.

Table 29–3. Enteral solutions.

Complete
Blenderized (eg, Compleat Regular, Compleat Modified ¹)
Whole protein, lactose-containing (eg, Carnation Instant Breakfast)
Whole protein, lactose-free, low-residue:
1 kcal/mL (eg, Ensure, Isocal, Osmolite, Nutren 1.0, ¹ Sustacal, Resource)
1.5 kcal/mL (eg, Ensure Plus, Comply, Nutren 1.5, Resource Plus)
2 kcal/mL (eg, Isocal HN, Magnacal, TwoCal HN)
High-nitrogen: > 15% total calories from protein (eg, Ensure HN, Osmolite HN, ¹ Replete, Isocal HN, ¹ Isosource HN, ¹)
Whole protein, lactose-free, high-residue:
1 kcal/mL (eg, Jevity, ¹ Nutren 1.0 with fiber, ¹ Fibersource HN)
Chemically defined peptide- or amino acid-based (eg, Peptamen, ¹ Vital HN, AlitraQ, Tolerex, Vivonex TEN)
"Disease-specific" formulas
Advanced chronic kidney disease: with essential amino acids (eg, Amin-Aid, Magnacal, Nepro, Nepro Carb Steady, Suplena, Traversorb Renal, Novasource Renal, Renalcal)
Type 2 diabetes: with lower carbohydrate content (eg, Glucerna, Glucerna Select, Glucerna 1.2, Glucerna 1.5, Glytrol, Diabeti-source AC)
Malabsorption: with medium-chain triglycerides (eg, Portagen, ¹ Traversorb MCT)
Respiratory failure: with > 50% calories from fat (eg, Pulmocare, NutriVent, Nutren Pulmonary)
Hepatic encephalopathy: with high amounts of branched-chain amino acids (eg, Hepatic-Aid II, Nutri-Hep)
Wound healing: with high protein content (eg, Promote, Replete)
Incomplete (modular)
Protein (eg, ProMod, Propac); protein supplements (eg, ProStat Sugar Free, Beneprotein, Unjury)
Carbohydrate (eg, Polycole, SolCarb)
Fat (eg, MCT Oil, Microlipid)

¹Isotonic.

Solutions containing hydrolyzed proteins or crystalline amino acids and with no significant fat content are called elemental solutions, since macronutrients are provided in their most “elemental” form. These solutions have been designed for patients with malabsorption, particularly pancreatic insufficiency and limited fat absorption. Elemental diets are extremely hypertonic and often result in more severe diarrhea. Their use should be limited to patients who cannot tolerate isotonic solutions.

Although formulas have been designed for specific clinical situations—solutions containing primarily essential amino acids (for advanced chronic kidney disease), medium-chain triglycerides (for fat malabsorption), more fat (for respiratory failure and CO₂ retention), and more branched-chain amino acids (for hepatic encephalopathy and severe trauma)—they have not been shown to be superior to standard formulas for most patients.

Enteral solutions should be administered via continuous infusion, preferably with an infusion pump. Isotonic feedings should be started at full strength at about 25–33% of the estimated final infusion rate. Feedings can be advanced by similar amounts every 12 hours as tolerated. Hypertonic feedings should be started at half strength. The strength and the rate can then be advanced every 6 hours as tolerated.

COMPLICATIONS OF ENTERAL NUTRITIONAL SUPPORT

Minor complications of enteral nutritional support occur in 10–15% of patients. Gastrointestinal complications include diarrhea (most common), inadequate gastric emptying, emesis, esophagitis, and occasionally gastrointestinal bleeding. Diarrhea associated with enteral nutritional support may be due to intolerance to the osmotic load or to one of the macronutrients (eg, fat, lactose) in the solution. Patients being fed in this way may also have diarrhea from other causes (as side effects of antibiotics or other drugs, associated with infection, etc), and these possibilities should be investigated in appropriate circumstances.

Mechanical complications of enteral nutritional support are potentially the most serious. Of particular importance is aspiration. All patients receiving nasogastric tube feedings are at risk for this life-threatening complication. Limiting nasogastric feedings to those patients who can adequately protect their airway and careful monitoring of patients fed by tube should limit these serious complications to 1–2% of cases. Minor mechanical complications are common and include tube obstruction and dislodgment.

Metabolic complications during enteral nutritional support are common but are easily managed in most cases. The most important problem is hypernatremic dehydration, most commonly seen in elderly patients given excessive protein intake who are unable to respond to thirst. Abnormalities of potassium, glucose, CO₂ production, and acid–base balance may also occur.

Lewis SR et al. Enteral versus parenteral nutrition and enteral versus a combination of enteral and parenteral nutrition for adults in the intensive care unit. Cochrane Database Syst Rev. 2018;6:CD012276. [PMID: 29883514]

Shi J et al. Effect of combined parenteral and enteral nutrition versus enteral nutrition alone for critically ill patients: a systematic review and meta-analysis. Medicine (Baltimore). 2018;97:e11874. [PMID: 30313021]

Zhang G et al. The effect of enteral versus parenteral nutrition for critically ill patients: a systematic review and meta-analysis. J Clin Anesth. 2018;51:62. [PMID: 30098572]

PARENTERAL NUTRITIONAL SUPPORT SOLUTIONS

Parenteral nutritional support solutions can be designed to deliver adequate nutrients to most patients. The basic parenteral solution is composed of dextrose, amino acids, and water. Electrolytes, minerals, trace elements, vitamins, and medications can also be added. Most commercial solutions contain the monohydrate form of dextrose that provides 3.4 kcal/g. Crystalline amino acids are available in a variety of concentrations, so that a broad range of solutions can be made to contain specific amounts of dextrose and amino acids as required.

Typical solutions for central vein nutritional support contain 25–35% dextrose and 2.75–6% amino acids depending on the patient's estimated nutrient and water requirements. These solutions generally have osmolalities in excess of 1800 mOsm/L and require infusion into a central vein. A typical formula for patients without organ failure is shown in Table 29–4.

Solutions with lower osmolalities can also be designed for infusion into peripheral veins. Solutions for peripheral infusion usually contain 5–10% dextrose and 2.75–4.25%

Table 29–4. Typical parenteral nutrition solution (for stable patients without organ failure).

Dextrose (3.4 kcal/g)	25%
Amino acids (4 kcal/g)	6%
Na ⁺	50 mEq/L
K ⁺	40 mEq/L
Ca ²⁺	5 mEq/L
Mg ²⁺	8 mEq/L
Cl ⁻	60 mEq/L
P	12 mEq/L
Acetate	Balance
MVI-12 (vitamins)	10 mL/day
MTE (trace elements)	5 mL/day
Fat emulsion 20%	250 mL two to seven times per week (depending on caloric requirements)
Typical rate	Day 1: 30 mL/h Day 2: 60 mL/h
By day 2, solution provides:	Calories: 1925 kcal total Protein: 86 g Fat: 19% of total kcal Fluid: 1690 mL

amino acids. These solutions have osmolalities between 800 and 1200 mOsm/L and result in a high incidence of thrombophlebitis and line infiltration. These solutions will provide adequate protein for most patients but inadequate energy. Additional energy must be provided in the form of emulsified soybean or safflower oil. Such intravenous fat solutions are currently available in 10% and 25% solutions providing 1.1 and 2.2 kcal/mL, respectively. Intravenous fat solutions are isosmotic and well tolerated by peripheral veins.

Typical patients are given 200–500 mL of a 20% solution each day. As much as 60% of total calories can be administered in this manner.

Intravenous fat can also be provided to patients receiving central vein nutritional support. In this instance, dextrose concentrations should be decreased to provide a fixed concentration of energy. Intravenous fat is associated with less glucose intolerance, less production of carbon dioxide, and less fatty infiltration of the liver and has been increasingly utilized in patients with hyperglycemia, respiratory failure, and liver disease. Intravenous fat has also been increasingly used in patients with large estimated energy requirements. The maximum glucose utilization rate is approximately 5–7 mg/min/kg. Patients who require additional calories can be given them as fat to prevent excess administration of dextrose. Intravenous fat can also be used to prevent essential fatty acid deficiency. The optimal ratio of carbohydrate and fat in parenteral nutritional support has not been determined.

Infusion of parenteral solutions should be started slowly to prevent hyperglycemia and other metabolic complications. Typical solutions are given initially at a rate of 50 mL/h and advanced by about the same amount every 24 hours until the desired final rate is reached.

Burden S et al. The impact of home parenteral nutrition on the burden of disease including morbidity, mortality and rate of hospitalisations. *Clin Nutr ESPEN*. 2018;28:222. [PMID: 30390885]

Kovacevich DS et al. American Society for Parenteral and Enteral Nutrition guidelines for the selection and care of central venous access devices for adult home parenteral nutrition administration. *JPEN J Parenter Enteral Nutr*. 2019;43:15. [PMID: 30339287]

Russell MK et al. Supplemental parenteral nutrition: review of the literature and current nutrition guidelines. *Nutr Clin Pract*. 2018;33:359. [PMID: 29878557]

COMPLICATIONS OF PARENTERAL NUTRITIONAL SUPPORT

Complications of central vein nutritional support occur in up to 50% of patients. Although most are minor and easily managed, significant complications develop in approximately 5% of patients. Complications of central vein nutritional support can be divided into catheter-related complications and metabolic complications.

Catheter-related complications can occur during insertion or while the catheter is in place. Pneumothorax, hemothorax, arterial laceration, air emboli, and brachial plexus injury can occur during catheter placement. The incidence of these complications is inversely related to the experience of the clinician performing the procedure but occur in at least 1–2% of cases even in major medical centers. Each catheter placement should be documented by chest radiograph prior to initiation of nutritional support.

Catheter thrombosis and catheter-related sepsis are the most important complications of indwelling catheters. Patients with indwelling central vein catheters in whom fever develops without an apparent source should have their lines changed over a wire or removed immediately, the tip quantitatively cultured, and antibiotics begun empirically. Quantitative tip cultures and blood cultures help guide further antibiotic therapy. Catheter-related sepsis occurs in 2–3% of patients even if optimal efforts are made to prevent infection.

Metabolic complications of central vein nutritional support occur in over 50% of patients (Table 29–5). Most are minor and easily managed, and termination of support is seldom necessary.

Kovacevich DS et al. American Society for Parenteral and Enteral Nutrition guidelines for the selection and care of central venous access devices for adult home parenteral nutrition administration. *JPEN J Parenter Enteral Nutr*. 2019;43:15. [PMID: 30339287]

Table 29–5. Metabolic complications of parenteral nutritional support.

Complication	Common Causes	Possible Solutions
Hyperglycemia	Too rapid infusion of dextrose, "stress," corticosteroids	Decrease glucose infusion; insulin; replacement of dextrose with fat
Hyperosmolar nonketotic dehydration	Severe, undetected hyperglycemia	Insulin, hydration, potassium
Hyperchloremic metabolic acidosis	High chloride administration	Decrease chloride
Azotemia	Excessive protein administration	Decrease amino acid concentration
Hyperphosphatemia, hypokalemia, hypomagnesemia	Extracellular to intracellular shifting with refeeding	Increase solution concentration
Liver enzyme abnormalities	Lipid trapping in hepatocytes, fatty liver	Decrease dextrose
Acalculous cholecystitis	Biliary stasis	Oral fat
Zinc deficiency	Diarrhea, small bowel fistulas	Increase concentration
Copper deficiency	Biliary fistulas	Increase concentration

Santacruz E et al. Infectious complications in home parenteral nutrition: a long-term study with peripherally inserted central catheters, tunneled catheters, and ports. *Nutrition*. 2019;58:89. [PMID: 30391696]

PATIENT MONITORING DURING NUTRITIONAL SUPPORT

Every patient receiving enteral or parenteral nutritional support should be monitored closely. Formal nutritional support teams composed of a physician, a nurse, a dietitian, and a pharmacist have been shown to decrease the rate of complications.

Patients should be monitored both for the adequacy of treatment and to prevent and detect complications. Because estimates of nutritional requirements are imprecise, frequent reassessment is necessary. Daily intakes should be recorded and compared with estimated requirements. Body weight, hydration status, and overall clinical status should be followed. Patients who do not appear to be responding as anticipated can be evaluated for nitrogen balance by means of the following equation:

$$\text{Nitrogen balance} = \frac{\text{24-hour protein intake (g)}}{6.25} - \left(\frac{\text{24-hour urinary nitrogen (g)}}{} + 4 \right)$$

Patients with positive nitrogen balances can be continued on their current regimens. Patients with negative balances should receive moderate increases in calorie and protein intake and reassessed. Monitoring for metabolic complications includes daily laboratory tests including serum glucose, sodium, chloride, potassium, phosphorus, magnesium, calcium, creatinine, and BUN. Once the patient is stabilized, these tests should be obtained at least twice weekly. Red blood cell folate, zinc, and copper should be checked at least monthly.

Hellerman Itzhaki M et al. Advances in medical nutrition therapy: parenteral nutrition. *Nutrients*. 2020;12:717. [PMID: 32182654]

Kopp Lugli A et al. Medical nutrition therapy in critically ill patients treated on intensive and intermediate care units: a literature review. *J Clin Med*. 2019;8:1395. [PMID: 31500087]

Lambell KJ et al. Nutrition therapy in critical illness: a review of the literature for clinicians. *Crit Care*. 2020;24:35. [PMID: 32019607]

30

Common Problems in Infectious Diseases & Antimicrobial Therapy

Peter V. Chin-Hong, MD

B. Joseph Guglielmo, PharmD

COMMON PROBLEMS IN INFECTIOUS DISEASES

FEVER OF UNKNOWN ORIGIN (FUO)



ESSENTIALS OF DIAGNOSIS

- ▶ Illness of at least 3 weeks in duration.
- ▶ Fever $> 38.3^{\circ}\text{C}$ on several occasions.
- ▶ Diagnosis has not been made after three outpatient visits or 3 days of hospitalization.

► General Considerations

The intervals specified in the criteria for the diagnosis of FUO are arbitrary ones intended to exclude patients with protracted but self-limited viral illnesses and to allow time for the usual radiographic, serologic, and cultural studies to be performed. The criteria for FUO are met when a diagnosis has not been made after three outpatient visits or 3 days of hospitalization.

Added categories of FUO include complications of current health care scenarios: (1) **Hospital-associated FUO** refers to the hospitalized patient with fever of 38.3°C or higher on several occasions, due to a process not present or incubating at the time of admission, in whom initial cultures are negative and the diagnosis remains unknown after 3 days of investigation (see Health Care-Associated Infections below); (2) **neutropenic FUO** includes patients with fever of 38.3°C or higher on several occasions with less than 500 neutrophils per microliter in whom initial cultures are negative and the diagnosis remains uncertain after 3 days (see Chapter 2 and Infections in the Immunocompromised Patient, below); (3) **HIV-associated FUO** pertains to HIV-positive patients with fever of 38.3°C or higher who have been febrile for 4 weeks or more as an outpatient or 3 days as an inpatient, in whom the diagnosis remains uncertain after 3 days of investigation with at least 2 days for cultures to incubate (see Chapter 31). Although not usually considered separately, **FUO in solid organ**

transplant recipients and **FUO in the returning traveler** are common scenarios, each with a unique differential diagnosis, and are also discussed in this chapter.

For a general discussion of fever, see the section on fever and hyperthermia in Chapter 2.

A. Common Causes

Most cases represent unusual manifestations of common diseases and not rare or exotic diseases—eg, tuberculosis, endocarditis, gallbladder disease, and HIV (primary infection or opportunistic infection) are more common causes of FUO than Whipple disease or familial Mediterranean fever.

B. Age of Patient

In adults, infections (25–40% of cases) and cancer (25–40% of cases) account for the majority of FUOs. In children, infections are the most common cause of FUO (30–50% of cases) and cancer a rare cause (5–10% of cases). Autoimmune disorders occur with equal frequency in adults and children (10–20% of cases), but the diseases differ. Juvenile rheumatoid arthritis is particularly common in children, whereas systemic lupus erythematosus, granulomatosis with polyangiitis, and polyarteritis nodosa are more common in adults. Still disease, giant cell arteritis, and polymyalgia rheumatica occur exclusively in adults. In adults over 65 years of age, multisystem immune-mediated diseases such as temporal arteritis, polymyalgia rheumatica, sarcoidosis, rheumatoid arthritis, and granulomatosis with polyangiitis account for 25–30% of all FUOs.

C. Duration of Fever

The cause of FUO changes dramatically in patients who have been febrile for 6 months or longer. Infection, cancer, and autoimmune disorders combined account for only 20% of FUOs in these patients. Instead, other entities such as granulomatous diseases (granulomatous hepatitis, Crohn disease, ulcerative colitis) and factitious fever become important causes. One-fourth of patients who say they have been febrile for 6 months or longer actually have no true fever or underlying disease. Instead, the usual normal circadian variation in temperature (temperature

0.5–1°C higher in the afternoon than in the morning) is interpreted as abnormal. Patients with **episodic** or **recurrent fever** (ie, those who meet the criteria for FUO but have fever-free periods of 2 weeks or longer) are similar to those with **prolonged fever**. Infection, malignancy, and autoimmune disorders account for only 20–25% of such fevers, whereas various miscellaneous diseases (Crohn disease, familial Mediterranean fever, allergic alveolitis) account for another 25%. *Approximately 50% of cases remain undiagnosed but have a benign course with eventual resolution of symptoms.*

D. Immunologic Status

In the neutropenic patient, fungal infections and occult bacterial infections are important causes of FUO. In the patient taking immunosuppressive medications (particularly organ transplant patients), cytomegalovirus (CMV) infections are a frequent cause of fever, as are fungal infections, nocardiosis, *Pneumocystis jirovecii* pneumonia, and mycobacterial infections.

E. Classification of Causes of FUO

Most patients with FUO will fit into one of five categories.

1. Infection—Both systemic and localized infections can cause FUO. Tuberculosis and endocarditis are the most common systemic infections associated with FUO, but mycoses, viral diseases (particularly infection with Epstein-Barr virus and CMV), toxoplasmosis, brucellosis, Q fever, cat-scratch disease, salmonellosis, malaria, and many other less common infections have been implicated. Primary infection with HIV or opportunistic infections associated with AIDS—particularly mycobacterial infections—can also present as FUO. The most common form of localized infection causing FUO is an occult abscess. Liver, spleen, kidney, brain, and bone abscesses may be difficult to detect. A collection of pus may form in the peritoneal cavity or in the subdiaphragmatic, subhepatic, paracolic, or other areas. Cholangitis, osteomyelitis, urinary tract infection, dental abscess, or paranasal sinusitis may cause prolonged fever.

2. Neoplasms—Many cancers can present as FUO. The most common are lymphoma (both Hodgkin and non-Hodgkin) and leukemia. Posttransplant lymphoproliferative disorders may also present with fever. Other diseases of lymph nodes, such as angioimmunoblastic lymphoma and Castleman disease, can also cause FUO. Primary and metastatic tumors of the liver are frequently associated with fever, as are renal cell carcinomas. Atrial myxoma is an often forgotten neoplasm that can result in fever. Chronic lymphocytic leukemia and multiple myeloma are rarely associated with fever, and the presence of fever in patients with these diseases should prompt a search for infection.

3. Autoimmune disorders—Still disease, systemic lupus erythematosus, cryoglobulinemia, and polyarteritis nodosa are the most common causes of autoimmune-associated FUO. Giant cell arteritis and polymyalgia rheumatica are seen almost exclusively in patients over 50 years of age and

are nearly always associated with an elevated erythrocyte sedimentation rate (greater than 40 mm/h).

4. Miscellaneous causes—Many other conditions have been associated with FUO but less commonly than the foregoing types of illness. Examples include thyroiditis, sarcoidosis, Whipple disease, familial Mediterranean fever, recurrent pulmonary emboli, alcoholic hepatitis, drug fever, and factitious fever.

5. Undiagnosed FUO—Despite extensive evaluation, the diagnosis remains elusive in 15% or more of patients. Of these patients, the fever abates spontaneously in about 75% with no diagnosis; in the remainder, more classic manifestations of the underlying disease appear over time.

Clinical Findings

Because the evaluation of a patient with FUO is costly and time-consuming, it is imperative to first document the presence of fever. This is done by observing the patient while the temperature is being taken to ascertain that fever is not factitious (self-induced). Associated findings that accompany fever include tachycardia, chills, and piloerection. A thorough history—including family, occupational, social (sexual practices, use of injection drugs), dietary (unpasteurized products, raw meat), exposures (animals, chemicals), and travel—may give clues to the diagnosis. Repeated physical examination may reveal subtle, evanescent clinical findings essential to diagnosis.

A. Laboratory Tests

In addition to routine laboratory studies, blood cultures should always be obtained, preferably when the patient has not taken antibiotics for several days, and should be held by the laboratory for 2 weeks to detect slow-growing organisms. Cultures on special media are requested if *Legionella*, *Bartonella*, or nutritionally deficient streptococci are possible pathogens. “Screening tests” with immunologic or microbiologic serologies (“febrile agglutinins”) are of low yield and should *not* be done. If the history or physical examination suggests a specific diagnosis, specific serologic tests with an associated fourfold rise or fall in titer may be useful. Because infection is the most common cause of FUO, other body fluids are usually cultured, ie, urine, sputum, stool, cerebrospinal fluid, and morning gastric aspirates (if one suspects tuberculosis). Direct examination of blood smears may establish a diagnosis of malaria or relapsing fever (*Borrelia*).

B. Imaging

All patients with FUO should have a chest radiograph. Studies such as sinus CT, upper gastrointestinal series with small bowel follow-through, barium enema, proctosigmoidoscopy, and evaluation of gallbladder function are reserved for patients who have symptoms, signs, or a history that suggest disease in these body regions. CT scan of the abdomen and pelvis is also frequently performed and is particularly useful for looking at the liver, spleen, and retroperitoneum. When the CT scan is abnormal, the findings often lead to a specific diagnosis. A normal CT scan is not

quite as useful; more invasive procedures such as biopsy or exploratory laparotomy may be needed. The role of MRI in the investigation of FUO has not been evaluated. In general, however, MRI is better than CT for detecting lesions of the nervous system and is useful in diagnosing various vasculitides. Ultrasound is sensitive for detecting lesions of the kidney, pancreas, and biliary tree. Echocardiography should be used if one is considering endocarditis or atrial myxoma. Transesophageal echocardiography is more sensitive than surface echocardiography for detecting valvular lesions, but even a negative transesophageal study does not exclude endocarditis (10% false-negative rate). The usefulness of radionuclide studies in diagnosing FUO is variable. Some experts use positron emission tomography (PET) if CT scans (chest and abdominal) are nondiagnostic early in the investigation of FUO. However, more studies are needed before this practice can be more fully integrated into clinical practice. In general, radionuclide scans are plagued by high rates of false-positive and false-negative results that are not useful when used as screening tests and, if done at all, are limited to those patients whose history or examination suggests local inflammation or infection.

C. Biopsy

Invasive procedures are often required for diagnosis. Any abnormal finding should be aggressively evaluated: Headache calls for lumbar puncture to rule out meningitis; skin rash should be biopsied for cutaneous manifestations of collagen vascular disease or infection; and enlarged lymph nodes should be aspirated or biopsied for neoplasm and sent for culture. Bone marrow aspiration with biopsy is a relatively low-yield procedure (15–25%; except in HIV-positive patients, in whom mycobacterial infection is a common cause of FUO), but the risk is low and the procedure should be done if other less invasive tests have not yielded a diagnosis, particularly in persons with hematologic abnormalities. Liver biopsy will yield a specific diagnosis in 10–15% of patients with FUO and should be considered in any patient with abnormal liver tests even if the liver is normal in size. CT scanning and MRI have decreased the need for exploratory laparotomy; however, surgical visualization and biopsies should be considered when there is continued deterioration or lack of diagnosis.

Treatment

Although an empiric course of antimicrobials is sometimes considered for FUO, it is *rarely* helpful and may impact infectious diseases diagnoses (eg, by reducing the sensitivity of blood cultures).

When to Refer

- Any patient with FUO and progressive weight loss and other constitutional signs.
- Any immunocompromised patient (eg, transplant recipients and HIV-infected patients).
- Infectious diseases specialists may also be able to coordinate and interpret specialized testing (eg, Q fever

serologies) with outside agencies, such as the US Centers for Disease Control and Prevention.

When to Admit

- Any patient who is rapidly declining with weight loss where hospital admission may expedite workup.
- If FUO is present in immunocompromised patients, such as those who are neutropenic from recent chemotherapy or those who have undergone transplantation (particularly in the previous 6 months).

Fusco FM et al. Fever of unknown origin (FUO): which are the factors influencing the final diagnosis? A 2005–2015 systematic review. *BMC Infect Dis*. 2019;19:653. [PMID: 31331269]

Mulders-Manders CM et al. Long-term prognosis, treatment, and outcome of patients with fever of unknown origin in whom no diagnosis was made despite extensive investigation: a questionnaire based study. *Medicine (Baltimore)*. 2018;97:e11241. [PMID: 29924054]

Wang WX et al. Combined clinical parameters improve the diagnostic efficacy of ¹⁸F-FDG PET/CT in patients with fever of unknown origin (FUO) and inflammation of unknown origin (IUO): a prospective study in China. *Int J Infect Dis*. 2020;93:77. [PMID: 31982625]

Zhai YZ et al. Clinical analysis of 215 consecutive cases with fever of unknown origin: a cohort study. *Medicine (Baltimore)*. 2018;97:e10986. [PMID: 29901588]

INFECTIONS IN THE IMMUNOCOMPROMISED PATIENT

ESSENTIALS OF DIAGNOSIS

- Fever and other symptoms may be blunted because of immunosuppression.
- A contaminating organism in an immunocompetent individual may be a pathogen in an immunocompromised one.
- The interval since transplantation and the degree of immunosuppression can narrow the differential diagnosis.
- Empiric broad-spectrum antibiotics may be appropriate in high-risk patients whether or not symptoms are localized.

General Considerations

Immunocompromised patients have defects in their natural defense mechanisms resulting in an increased risk for infection. In addition, infection is often severe, rapidly progressive, and life threatening. Organisms that are not usually problematic in the immunocompetent person may be important pathogens in the compromised patient (eg, *Staphylococcus epidermidis*, *Corynebacterium jeikeium*, *Propionibacterium acnes*, *Bacillus* species). Therefore, culture results must be interpreted with caution, and isolates should not be disregarded as solely contaminants. Although

the type of immunodeficiency is associated with specific infectious disease syndromes, *any pathogen can cause infection in any immunosuppressed patient at any time*. Thus, a systematic evaluation is required to identify a specific organism.

A. Impaired Humoral Immunity

Defects in humoral immunity are often congenital, although hypogammaglobulinemia can occur in multiple myeloma, chronic lymphocytic leukemia, small lymphocyte lymphoma, and in patients who have undergone splenectomy. Patients with ineffective humoral immunity lack opsonizing antibodies and are at particular risk for infection with *encapsulated organisms*, such as *Haemophilus influenzae*, *Neisseria meningitidis*, and *Streptococcus pneumoniae*. Although rituximab is normally thought of as being linked to impaired cellular immunity, it has been associated with the development of *Pneumocystis jirovecii* infection and progressive multifocal leukoencephalopathy (PML) as well as with hepatitis B reactivation.

B. Granulocytopenia (Neutropenia)

Granulocytopenia is common following hematopoietic cell transplantation (“stem cell transplantation”) and among patients with solid tumors—as a result of myelosuppressive chemotherapy—and in acute leukemias. *The risk of infection begins to increase when the absolute granulocyte count falls below 1000/mcL, with a dramatic increase in frequency and severity when the granulocyte count falls below 100/mcL*. The infection risk is also increased with a rapid rate of decline of neutrophils and with a prolonged period of neutropenia. The granulocytopenic patient is particularly susceptible to infections with gram-negative enteric organisms, *Pseudomonas*, gram-positive cocci (particularly *Staphylococcus aureus*, *S epidermidis*, and viridans streptococci), *Candida*, *Aspergillus*, and other fungi that have recently emerged as pathogens such as *Trichosporon*, *Scedosporium*, *Fusarium*, and the mucormycoses.

C. Impaired Cellular Immunity

Patients with cellular immune deficiency encompass a large and heterogeneous group, including patients with HIV infection (see Chapter 31); patients with lymphoreticular malignancies, such as Hodgkin disease; and patients receiving immunosuppressive medications, such as corticosteroids, cyclosporine, tacrolimus, and other cytotoxic medications. This latter group—those who are immunosuppressed as a result of medications—includes patients who have undergone solid organ transplantation, many patients receiving therapy for solid tumors, and patients receiving prolonged high-dose corticosteroid treatment (eg, for asthma, temporal arteritis, systemic lupus erythematosus). Patients taking tumor necrosis factor (TNF) inhibitors, such as etanercept and infliximab, are also included in this category. Patients with cellular immune dysfunction are susceptible to infections by a large number of organisms, particularly ones that replicate intracellularly. Examples include bacteria, such as *Listeria*, *Legionella*, *Salmonella*, and *Mycobacterium*; viruses, such as herpes

simplex, varicella, and CMV; fungi, such as *Cryptococcus*, *Coccidioides*, *Histoplasma*, and *Pneumocystis*; and protozoa, such as *Toxoplasma*.

D. Hematopoietic Cell Transplant Recipients

The length of time it takes for complications to occur in hematopoietic cell transplant recipients can be helpful in determining the etiologic agent. In the **early (preengraftment) posttransplant period** (days 1–21), patients will become severely neutropenic for 7–21 days. Patients are at risk for gram-positive (particularly catheter-related) and gram-negative bacterial infections, as well as herpes simplex virus, respiratory syncytial virus, and fungal infections. In contrast to solid organ transplant recipients, the source of fever is unknown in 60–70% of hematopoietic cell transplant patients. **Between 3 weeks and 3 months posttransplant**, infections with CMV, adenovirus, *Aspergillus*, and *Candida* are most common. *P jirovecii* pneumonia is possible, particularly in patients who receive additional immunosuppression for treatment of graft-versus-host disease. Patients continue to be at risk for infectious complications **beyond 3 months following transplantation**, particularly those who have received allogeneic transplantation and those who are taking immunosuppressive therapy for chronic graft-versus-host disease. Varicella-zoster is common, and *Aspergillus* and CMV infections are increasingly seen in this period as well.

E. Solid Organ Transplant Recipients

The length of time it takes for infection to occur following solid organ transplantation can also be helpful in determining the infectious origin. **Immediate postoperative infections** often involve the transplanted organ. Following lung transplantation, pneumonia and mediastinitis are particularly common; following liver transplantation, intra-abdominal abscess, cholangitis, and peritonitis may be seen; after kidney transplantation, urinary tract infections, perinephric abscesses, and infected lymphoceles can occur.

Most infections that occur in the **first 2–4 weeks post-transplant** are related to the operative procedure and to hospitalization itself (wound infection, intravenous catheter infection, urinary tract infection from an indwelling urinary [Foley] catheter) or are related to the transplanted organ. In rare instances, donor-derived infections (eg, West Nile virus, tuberculosis) may present during this time period. Compensated organ transplants obtained abroad through “medical tourism” can introduce additional risk of infections, which vary by country and by transplant setting. Infections that occur **between the first and sixth months** are often related to immunosuppression. During this period, reactivation of viruses, such as herpes simplex, varicella-zoster, and CMV is quite common. Opportunistic infections with fungi (eg, *Candida*, *Aspergillus*, *Cryptococcus*, *Pneumocystis*), *Listeria monocytogenes*, *Nocardia*, and *Toxoplasma* are also common. **After 6 months**, if immunosuppression has been reduced to maintenance levels, infections that would be expected in any population occur. Patients with poorly functioning allografts receiving

long-term immunosuppression therapy continue to be at risk for opportunistic infections.

F. Tumor Necrosis Factor Inhibitor Recipients

Patients taking TNF inhibitors (infliximab, etanercept, adalimumab, certolizumab pegol, golimumab) have specific defects that increase risk of bacterial, mycobacterial (particularly tuberculosis), viral (HBV reactivation and HCV progression), and fungal infections (*Pneumocystis*, molds, and endemic mycoses). Infection risk may be highest shortly after therapy is initiated (within the first 3 months) and with a higher dose of medications.

G. Recipients of Other Biologics

In addition to TNF inhibitors, other biologics target a variety of immunologic pathways that are involved in immunologic mediated disease and in cancer replication. Disruption of these pathways include, but are not limited to impact on B cells, T cells, complement, and leukocytes. This may result in not only serious infections, but the development of autoimmune disease and malignancies as well. Some medications have been observed to have specific associations with opportunistic infections (eg, natalizumab and PML, or eculizumab and meningococcal disease). Other biologics such as chimeric antigen receptor T (CAR-T) cells may have unintended infectious risks that are currently unknown, or may have adverse effects that mimic infection (eg, cytokine release syndrome). Checkpoint inhibitors (eg, anti-PD-1 and CTLA antibodies) used for the treatment of advanced malignancies also may have effects that mimic infection via immune enhancement. Prolonged immunosuppression used to treat immune-associated adverse events in CAR-T and checkpoint inhibitor therapy (eg, TNF inhibitors and corticosteroids) can then result in opportunistic and other infections. As more biologics are developed and used, clinicians must remain vigilant for the possibility of serious infectious disease risk.

H. Other Immunocompromised States

A large group of patients who are not specifically immunodeficient are at increased risk for infection due to debilitating injury (eg, burns or severe trauma), invasive procedures (eg, chronic central intravenous catheters, indwelling urinary catheters, dialysis catheters), central nervous system (CNS) dysfunction (which predisposes patients to aspiration pneumonia and pressure injuries), obstructing lesions (eg, pneumonia due to an obstructed bronchus, pyelonephritis due to nephrolithiasis, cholangitis secondary to cholelithiasis), and use of broad-spectrum antibiotics. Patients with diabetes mellitus have alterations in cellular immunity, resulting in mucormycosis, emphysematous pyelonephritis, and foot infections.

Clinical Findings

A. Laboratory Findings

Routine evaluation includes complete blood count with differential, chest radiograph, and blood cultures; urine and respiratory cultures should be obtained if indicated

clinically or radiographically. Any focal complaints (localized pain, headache, rash) should prompt imaging and cultures appropriate to the site.

Patients who remain febrile without an obvious source should be evaluated for viral infection (serum CMV antigen test or polymerase chain reaction), abscesses (which usually occur near previous operative sites), candidiasis involving the liver or spleen, or aspergillosis. Serologic evaluation may be helpful if toxoplasmosis or an endemic fungal infection (coccidioidomycosis, histoplasmosis) is a possible cause. Antigen-based assays may be useful for the diagnosis of aspergillosis (detected by galactomannan level in serum or bronchoalveolar lavage fluid), or other invasive fungal disease, including *Pneumocystis* infection (serum [1→3]-beta-D-glucan level).

B. Special Diagnostic Procedures

Special diagnostic procedures should also be considered. The cause of pulmonary infiltrates can be easily determined with simple techniques in some situations—eg, induced sputum yields a diagnosis of *Pneumocystis* pneumonia in 50–80% of patients with AIDS with this infection. In other situations, more invasive procedures may be required (bronchoalveolar lavage, transbronchial biopsy, open lung biopsy). Skin, liver, or bone marrow biopsy may be helpful in establishing a diagnosis. Next generation DNA-sequencing analysis (eg, of plasma, bronchoalveolar lavage, cerebrospinal fluid) is an increasingly used and validated option for diagnosis of infectious diseases in immunocompromised persons.

Differential Diagnosis

Transplant rejection, organ ischemia and necrosis, thrombophlebitis, and lymphoma (posttransplant lymphoproliferative disease) may all present as fever and must be considered in the differential diagnosis.

Prevention

While prophylactic antimicrobial medications are used commonly, the optimal medications or dosage regimens are debated. Hand washing is the simplest and most effective means of decreasing hospital-associated infections, especially in the compromised patient. Invasive devices such as central and peripheral lines and indwelling urinary catheters are potential sources of infection. Some centers use laminar airflow isolation or high-efficiency particulate air (HEPA) filtering in hematopoietic cell transplant patients. Rates of infection and episodes of febrile neutropenia, but not mortality, are decreased if colony-stimulating factors are used (typically in situations where the risk of febrile neutropenia is 20% or higher) during chemotherapy or during stem-cell transplantation.

A. *Pneumocystis* & Herpes Simplex Infections

Trimethoprim-sulfamethoxazole (TMP-SMZ), one double-strength tablet orally three times a week, one double-strength tablet twice daily on weekends, or one single-strength tablet daily for 3–6 months can prevent

Pneumocystis infections in transplant patients. In patients allergic to TMP-SMZ, dapsone, 50 mg orally daily or 100 mg three times weekly, is recommended. Glucose-6-phosphate dehydrogenase (G6PD) levels should be assessed before dapsone is instituted. Acyclovir prevents herpes simplex infections in bone marrow and solid organ transplant recipients and is given to seropositive patients who are not receiving ganciclovir or valganciclovir for CMV prophylaxis. The usual dose is 200 mg orally three times daily for 4 weeks (hematopoietic cell transplants) to 12 weeks (other solid organ transplants).

B. CMV

No uniformly accepted approach has been adopted for prevention of CMV. Prevention strategies often depend on the serologic status of the donor and recipient and the organ transplanted, which determines the level of immunosuppression after transplant. In solid organ transplants (liver, kidney, heart, lung), the greatest risk of developing CMV disease is in seronegative recipients who receive organs from seropositive donors. These high-risk patients usually receive oral valganciclovir, 900 mg daily for 3–6 months (longer in lung transplant recipients). Other solid organ transplant recipients (seropositive recipients) are at lower risk for developing CMV disease, but still usually receive oral valganciclovir for 3 months. The lowest-risk group for the development of CMV disease is in seronegative patients who receive organs from seronegative donors. Typically, no CMV prophylaxis is used in this group. Ganciclovir and valganciclovir also prevent herpes virus reactivation. Because immunosuppression is increased during periods of rejection, patients treated for rejection usually receive CMV prophylaxis during rejection therapy. Increasingly popular is a preemptive management in which patients are monitored for the presence of CMV by polymerase chain reaction and other methodologies. If CMV is detected, then therapy is instituted with oral valganciclovir, 900 mg orally twice daily for a minimum of 2–3 weeks.

Recipients of hematopoietic cell transplants are more severely immunosuppressed than recipients of solid organ transplants, are at greater risk for developing serious CMV infection (usually CMV reactivation), and thus usually receive more aggressive prophylaxis. Like in solid organ transplant recipients, two approaches have been used: **universal prophylaxis or preemptive therapy**. In the former, all high-risk patients (seropositive patients who receive allogeneic transplants) may receive oral valganciclovir, 900 mg daily to day 100. However, valganciclovir is associated with significant bone marrow toxicity. Letermovir is being used increasingly, and it is not associated with bone marrow toxicity. Universal prophylaxis may be costly. Because of the possibility of bone marrow toxicity and the expense, many clinicians traditionally preferred the preemptive approach over the universal prophylaxis approach for recipients of hematopoietic stem cell transplants. However, while this preemptive approach is effective, it does miss a small number of patients in whom CMV disease would have been prevented had prophylaxis been used. Other preventive strategies include use of CMV-negative or

leukocyte-depleted blood products for CMV-seronegative recipients.

C. Other Organisms

Routine decontamination of the gastrointestinal tract to prevent bacteremia in the neutropenic patient is *not* recommended. The use of prophylactic antibiotics in the afebrile, asymptomatic neutropenic patient is debated, although many centers have adopted this strategy. Rates of bacteremia are decreased, but overall mortality is not affected and emergence of resistant organisms takes place. Use of intravenous immunoglobulin is reserved for the small number of patients with severe hypogammaglobulinemia following hematopoietic stem cell transplantation and should not be routinely administered to all transplant patients.

Prophylaxis with antifungal agents to prevent invasive mold (primarily *Aspergillus*) and yeast (primarily *Candida*) infections is routinely used, but the optimal agent, dose, and duration are also debated. Lipid-based preparations of amphotericin B, aerosolized amphotericin B, intravenous and oral fluconazole or voriconazole, and oral posaconazole solution and tablets are all prophylactic options in the neutropenic patient. Voriconazole is superior to amphotericin for documented *Aspergillus* infections, and posaconazole prophylaxis (compared with fluconazole) results in fewer cases of invasive aspergillosis among allogeneic stem cell transplant recipients with graft-versus-host disease; thus, one approach to prophylaxis is to use oral fluconazole (400 mg/day) for patients at low risk for developing fungal infections (autologous stem cell transplants) and oral voriconazole (200 mg twice daily) or oral posaconazole (200 mg suspension three times daily or 300 mg [three 100-mg tablets] sustained-release tablets once daily) for those at high risk (allogeneic transplants, graft-versus-host disease) at least until engraftment (usually 30 days). In solid organ transplant recipients, the risk of invasive fungal infection varies considerably (1–2% in liver, pancreas, and kidney transplants and 6–8% in heart and lung transplants). Whether universal prophylaxis or observation with preemptive therapy is the best approach has not been determined. Although fluconazole is effective in preventing yeast infections, emergence of fluconazole-resistant *Candida* and molds (*Fusarium*, *Aspergillus*, *Mucor*) has raised concerns about its routine use as a prophylactic agent in the general solid organ transplant population. However, liver transplant recipients with additional risk factors, such as having undergone a choledochojejunostomy, having had a high transfusion requirement or having developed kidney disease, may benefit from abbreviated postoperative *Candida* prophylaxis.

Given the high risk of reactivation of tuberculosis in patients taking TNF inhibitors, *all patients should be screened for latent tuberculosis infection (LTBI)* with a tuberculin skin test or an interferon-gamma release assay prior to the start of therapy. If LTBI is diagnosed, treatment with the TNF inhibitors should be delayed until treatment for LTBI is completed. There is also a marked risk of reactivation of hepatitis B and hepatitis C in patients taking TNF inhibitors; patients should also be screened for these

viruses when TNF inhibitor treatment is being considered. Providers should also ensure that patients' vaccinations are up-to-date before starting TNF inhibitors therapy.

► Treatment

A. General Measures

Because infections in the immunocompromised patient can be rapidly progressive and life-threatening, diagnostic procedures must be performed promptly, and empiric therapy is usually instituted.

While reduction or discontinuation of immunosuppressive medication may jeopardize the viability of the transplanted organ, this measure may be necessary if the infection is life-threatening. Hematopoietic growth factors (granulocyte and granulocyte-macrophage colony-stimulating factors) stimulate proliferation of bone marrow stem cells, resulting in an increase in peripheral leukocytes. These agents shorten the period of neutropenia and have been associated with reduction in infection.

B. Specific Measures

Antimicrobial medication therapy ultimately should be tailored to culture results. While combinations of antimicrobials are used with the intent of providing synergy or preventing resistance, the primary reason for empiric combination therapy is broad-spectrum coverage of all likely pathogens.

Empiric therapy is often instituted at the earliest sign of infection in the immunosuppressed patient because prompt therapy favorably affects outcome, particularly in febrile neutropenia. The antibiotic or combination of antibiotics used depends on the degree of immune compromise and the site of infection. For example, in the febrile neutropenic patient, an **algorithmic approach** to therapy is often used. Febrile neutropenic patients should be empirically treated with broad-spectrum agents active against selected gram-positive bacteria, *Pseudomonas aeruginosa*, and other aerobic gram-negative bacilli (such as cefepime 2 g every 8 hours intravenously). The addition of vancomycin, 10–15 mg/kg/dose intravenously every 12 hours, should be considered in those patients with suspected infection due to methicillin-resistant *Staphylococcus aureus* (MRSA), *S epidermidis*, enterococcus, and resistant viridans streptococci. Continued neutropenic fever necessitates broadening of antibacterial coverage from cefepime to agents such as imipenem 500 mg every 6 hours or meropenem 1 g every 8 hours intravenously with or without tobramycin 5–7 mg/kg intravenously every 24 hours. Antifungal agents (such as voriconazole, 200 mg intravenously or orally every 12 hours, or caspofungin, 50 mg daily intravenously) should be added if fevers continue after 5–7 days of broad-spectrum antibacterial therapy. Regardless of whether the patient becomes afebrile, *therapy is usually continued until resolution of neutropenia*. There is some evidence to support earlier discontinuation of antibiotics in the neutropenic patient who becomes afebrile if no signs or symptoms of infection persist.

Patients with fever and low-risk neutropenia (neutropenia expected to persist for less than 10 days, no comorbid complications requiring hospitalization, and cancer

adequately treated) can be treated with oral antibiotic regimens, such as ciprofloxacin, 750 mg every 12 hours, plus amoxicillin-clavulanic acid, 500 mg every 8 hours. Antibiotics are usually continued as long as the patient is neutropenic even if a source is not identified. In the organ transplant patient with interstitial infiltrates, the main concern is infection with *Pneumocystis* or *Legionella* species, so that empiric treatment with a macrolide or fluoroquinolone (*Legionella*) and TMP-SMZ, 15 mg/kg/day orally or intravenously, based on trimethoprim component (*Pneumocystis*) would be reasonable in those patients not receiving TMP-SMZ prophylaxis. If the patient does not respond to empiric treatment, a decision must be made to add more antimicrobial agents or perform invasive procedures (see above) to make a specific diagnosis. By making a definite diagnosis, therapy can be specific, thereby reducing selection pressure for resistance and superinfection.

► When to Refer

- Any immunocompromised patient with an opportunistic infection.
- Patients with potential drug toxicities and drug interactions related to antimicrobials where alternative agents are sought.
- Patients with latent tuberculosis, HBV, and HCV infection in whom therapy with TNF inhibitors is planned.

► When to Admit

Immunocompromised patients who are febrile, or those without fevers in whom an infection is suspected, particularly in the following groups: solid-organ or hematopoietic stem cell transplant recipient (particularly in the first 6 months), neutropenic patients, patients receiving TNF inhibitors, and transplant recipients who have had recent rejection episodes (including graft-versus-host disease).

- Durand CM et al. Four-week direct-acting antiviral prophylaxis for kidney transplantation from hepatitis C-viremic donors to hepatitis C-negative recipients: an open-label nonrandomized study. Ann Intern Med. 2021;174:137. [PMID: 32894697]
- Fung M et al. Plasma cell-free DNA Next-generation sequencing to diagnose and monitor infections in allogeneic hematopoietic stem cell transplant patients. Open Forum Infect Dis. 2018;5:ofy301. [PMID: 3051881]
- Hamandi B et al. Voriconazole and squamous cell carcinoma after lung transplantation: a multicenter study. Am J Transplant. 2018;18:113. [PMID: 28898527]
- Hogan CA et al. Clinical impact of metagenomic next-generation sequencing of plasma cell-free DNA for the diagnosis of infectious diseases: a multicenter retrospective cohort study. Clin Infect Dis. 2021;72:239. [PMID: 31942944]
- Selhorst P et al. Longer-term outcomes of HIV-positive-to-HIV-positive renal transplantation. N Engl J Med. 2019;381:1387. [PMID: 31577883]
- Van de Wyngaert Z et al. Discontinuation of antimicrobial therapy in adult neutropenic haematology patients: a prospective cohort. Int J Antimicrob Agents. 2019;53:781. [PMID: 30831232]
- Wilk AR et al. National landscape of HIV+ to HIV+ kidney and liver transplantation in the United States. Am J Transplant. 2019;19:2594. [PMID: 31207040]

HEALTH CARE-ASSOCIATED INFECTIONS



ESSENTIALS OF DIAGNOSIS

- ▶ Acquired during the course of receiving health care treatment for other conditions.
- ▶ Most cases are preventable.
- ▶ Hospital-associated infections are defined as not being present or incubating at the time of hospital admission and developing ≥ 48 hours after admission.
- ▶ Hand washing is the most effective prevention and should be done routinely even when gloves are worn.

► General Considerations

Worldwide, approximately 10% of patients acquire a health care-associated infection, resulting in prolongation of the hospital stay, increase in cost of care, and significant morbidity and mortality. The most common infections are urinary tract infections, usually associated with indwelling urinary catheters or urologic procedures; bloodstream infections, most commonly from indwelling catheters but also from secondary sites, such as surgical wounds, abscesses, pneumonia, the genitourinary tract, and the gastrointestinal tract; pneumonia in intubated patients or those with altered levels of consciousness; surgical wound infections; MRSA infections; and *Clostridioides difficile* colitis.

Some general principles are helpful in preventing, diagnosing, and treating health care-associated infections:

1. Many infections are a direct result of the use of *invasive devices* for monitoring or therapy, such as intravenous catheters, indwelling urinary catheters, shunts, surgical drains, catheters placed by interventional radiology for drainage, nasogastric tubes, and orotracheal or nasotracheal tubes for ventilatory support. *Early removal of such devices reduces the possibility of infection.*
2. Patients in whom health care-associated infections develop are often critically ill, have been hospitalized for extended periods, and have received several courses of broad-spectrum antibiotic therapy. As a result, health care-associated infections are often due to *multidrug resistant pathogens* and differ from those encountered in community-acquired infections. For example, *S aureus* and *S epidermidis* (a frequent cause of prosthetic device infection) are often resistant to methicillin and most cephalosporins (ceftaroline is the only active cephalosporin against MRSA) and require vancomycin for therapy; *Enterococcus faecium* resistant to ampicillin and vancomycin; gram-negative infections caused by *Pseudomonas*, *Citrobacter*, *Enterobacter*, *Acinetobacter*, *Stenotrophomonas*, extended-spectrum beta-lactamases (ESBL)-producing *E coli*, *Klebsiella*, and carbapenem-resistant Enterobacteriaceae (CRE) may be resistant to

most antibacterials. When choosing antibiotics to treat the seriously ill patient with a health care-associated infection, antimicrobial history and the “local ecology” must be considered. In the most seriously ill patients, broad-spectrum coverage with vancomycin and a carbapenem with or without an aminoglycoside is recommended. Once a pathogen is isolated and susceptibilities are known, the most narrow-spectrum, least toxic, most cost-effective regimen should be used.

Widespread use of antimicrobial medications contributes to the selection of drug-resistant organisms; thus, *every effort should be made to limit the spectrum of coverage and unnecessary duration*. All too often, unreliable or uninterpretable specimens are obtained for culture that result in unnecessary use of antibiotics. The best example of this principle is the diagnosis of line-related or bloodstream infection in the febrile patient. To avoid unnecessary use of antibiotics, thoughtful consideration of culture results is mandatory. A positive wound culture without signs of inflammation or infection, a positive sputum culture without pulmonary infiltrates on chest radiograph, or a positive urine culture in a catheterized patient without symptoms or signs of pyelonephritis are all likely to represent colonization, not infection.

► Clinical Findings

A. Symptoms and Signs

Catheter-associated infections have a variable presentation, depending on the type of catheter used (peripheral or central venous catheters, nontunneled or tunneled). Local signs of infection may be present at the insertion site, with pain, erythema, and purulence. Fever is often absent in uncomplicated infections and, if present, may indicate more disseminated disease such as bacteremia, cellulitis and septic thrombophlebitis. Often signs of infection at the insertion site are absent.

1. Fever in an intensive care unit patient—Fever complicates up to 70% of patients in intensive care units, and the etiology of the fever may be infectious or noninfectious. Common infectious causes include catheter-associated infections, hospital-acquired and ventilator-associated pneumonia (see Chapter 9), surgical site infections, urinary tract infections, and sepsis. Clinically relevant sinusitis is relatively uncommon in the patient in the intensive care unit.

An important noninfectious cause is thromboembolic disease. Fever in conjunction with refractory hypotension and shock may suggest sepsis; however, adrenal insufficiency, thyroid storm, and transfusion reaction may have a similar clinical presentation. Drug fever is difficult to diagnose and is usually a diagnosis of exclusion unless there are other signs of hypersensitivity, such as a typical maculopapular rash (most common with beta-lactams).

2. Fever in the postoperative patient—Postoperative fever is very common and noninfectious fever resolves spontaneously. Timing of the onset of the fever in relation to the surgical procedure may be of diagnostic benefit.

A. IMMEDIATE FEVER (IN THE FIRST FEW HOURS AFTER SURGERY)—Immediate fever can be due to medications that were given perioperatively, to surgical trauma, or to infections that were present before surgery. Necrotizing fasciitis due to group A streptococci or mixed organisms may present in this period. Malignant hyperthermia is rare and presents 30 minutes to several hours following inhalational anesthesia and is characterized by extreme hyperthermia, muscle rigidity, rhabdomyolysis, electrolyte abnormalities, and hypotension. Aggressive cooling and dantrolene are the mainstays of therapy. Aspiration of acidic gastric contents during surgery can result in a chemical pneumonitis (**Mendelson syndrome**) that develops rapidly, is transient, and does not require antibiotics. Fever due to surgical trauma usually resolves in 2–3 days; however, it may be longer in more complicated operative cases and in patients with head trauma.

B. ACUTE FEVER (WITHIN 1 WEEK OF SURGERY)—Acute fever is usually due to common causes of hospital-associated infections, such as ventilator-associated pneumonia (including aspiration pneumonia in patients with decreased gag reflex) and line infections. Noninfectious causes include alcohol withdrawal, gout, pulmonary embolism, and pancreatitis. Atelectasis following surgery is commonly invoked as a cause of postoperative fever but *there is no good evidence to support a causal association between the presence or degree of atelectasis and fever*.

C. SUBACUTE FEVER (AT LEAST 1 WEEK AFTER SURGERY)—Surgical site infections commonly present at least 1 week after surgery. The type of surgery that was performed predicts specific infectious etiologies. Patients undergoing cardiothoracic surgery may be at higher risk for pneumonia and deep and superficial sternal wound infections. Meningitis without typical signs of meningismus may complicate neurosurgical procedures. Postoperative deep abdominal abscesses may require drainage.

B. Laboratory Findings

Blood cultures are universally recommended, and chest radiographs are frequently obtained. A properly prepared sputum Gram stain and semi-quantitative sputum cultures may be useful in selected patients where there is a high pretest probability of pneumonia but multiple exclusion criteria probably limit generalizability in most patients, such as immunocompromised patients and those with drug resistance. Other diagnostic strategies will be dictated by the clinical context (eg, transesophageal echocardiogram in a patient with *S aureus* bacteremia).

Any fever in a patient with a central venous catheter should prompt the collection of blood. The best method to evaluate bacteremia is to gather *at least two peripherally obtained blood cultures*. Blood cultures from unidentified sites, a single blood culture from any site, or a blood culture through an existing line will often be positive for coagulase-positive staphylococci, particularly *S epidermidis*, often resulting in the inappropriate use of vancomycin. *Unless two separate venipuncture cultures are obtained—not through catheters—interpretation of results is impossible*, and unnecessary therapy often results. Each

“pseudobacteremia” increases bacterial resistance pressure, laboratory costs, antibiotic use, and length of stay. Microbiologic evaluation of the removed catheter can sometimes be helpful, but only in addition to (not instead of) blood cultures drawn from peripheral sites. The **differential time to positivity** measures the difference in time that cultures simultaneously drawn through a catheter and a peripheral site become positive. A positive test (at least 120 minutes’ difference in time) supports a catheter-related bloodstream infection, while a negative test suggests catheters may be retained.

► Complications

Complications such as septic thrombophlebitis, endocarditis, or metastatic foci of infection (particularly with *S aureus*) may be suspected in patients with persistent bacteremia and fever despite removal of the infected catheter. Additional studies such as venous Doppler studies, transesophageal echocardiogram, and chest radiographs may be indicated, and 4–6 weeks of antibiotics may be needed. In the case of septic thrombophlebitis, anticoagulation with heparin is also recommended if there are no contraindications.

► Differential Diagnosis

Although most fevers are due to infections, about 25% of patients will have fever of noninfectious origin, including drug fever, nonspecific postoperative fevers (tissue damage or necrosis), hematoma, pancreatitis, pulmonary embolism, myocardial infarction, and ischemic bowel disease.

► Prevention

The concept of **universal precautions** emphasizes that all patients are treated as though they have a potential blood-borne transmissible disease, and thus all body secretions are handled with care to prevent spread of disease. Body substance isolation requires use of gloves whenever a health care worker anticipates contact with blood or other body secretions. *Even though gloves are worn, health care workers should routinely wash their hands, since it is the easiest and most effective means of preventing hospital-associated infections.* Application of a rapid drying, alcohol-based antiseptic is simple, takes less time than traditional hand washing with soap and water, is more effective at reducing hand colonization, and promotes compliance with hand decontamination. For prevention of transmission of *C difficile* infection, hand washing is *more effective than alcohol-based antiseptics*. Consequently, even after removing gloves, providers should always wash hands in cases of proven or suspected *C difficile* infection.

Peripheral intravenous lines should be replaced no more frequently than every 3–4 days. Some clinicians replace only when clinically indicated or if the line was put in emergently. Arterial lines and lines in the central venous circulation (including those placed peripherally) can be left in place indefinitely and are changed or removed when they are clinically suspected of being infected, when they are nonfunctional, or when they are no longer needed.

Using sterile barrier precautions (including cap, mask, gown, gloves, and drape) is recommended while inserting central venous catheters. Antibiotic-impregnated (minocycline plus rifampin or chlorhexidine plus silver sulfadiazine) venous catheters reduce line infections. Silver alloy-impregnated indwelling urinary catheters reduce the incidence of catheter-associated bacteriuria, but not consistently catheter-associated urinary tract infections. Best practices to prevent ventilator-associated pneumonia include avoiding intubation if possible, minimizing and daily interruption of sedation, pooling/draining of subglottic secretions above the tube cuff, and elevating the head of the bed. Silver-coated endotracheal tubes may reduce the incidence of ventilator-associated pneumonia but has limited impact on hospital stay duration or mortality, so they are not generally recommended. Catheter-related urinary tract infections and intravenous catheter-associated infections are not Medicare-reimbursable conditions in the United States. Preoperative skin preparation with chlorhexidine and alcohol (versus povidone-iodine) reduces the incidence of infection following surgery. Another strategy that can prevent surgical-site infections is the identification and treatment of *S aureus* nasal carriers with 2% mupirocin nasal ointment and chlorhexidine soap. Daily bathing of ICU patients with chlorhexidine-impregnated washcloths versus soap and water results in lower incidence of health care–associated infections and colonization. Selective decontamination of the digestive tract with nonabsorbable or parenteral antibiotics, or both, may prevent hospital-acquired pneumonia and decrease mortality but is in limited use because of the concern of the development of antibiotic resistance. **Prevention bundles** (implementing more than one intervention concomitantly) are commonly used as a practical strategy to enhance care.

Attentive nursing care (positioning to prevent pressure injuries, wound care, elevating the head during tube feedings to prevent aspiration) is critical in preventing hospital-associated infections. In addition, monitoring of high-risk areas by hospital epidemiologists is critical in the prevention of infection. Some guidelines advocate rapid screening (active surveillance cultures) for MRSA on admission to acute care facilities among certain subpopulations of patients (eg, those recently hospitalized, admission to the intensive care unit, patients undergoing hemodialysis). However, outside the setting of an MRSA outbreak, it is not clear whether this strategy decreases the incidence of hospital-associated MRSA infections.

Vaccines, including hepatitis A, hepatitis B, and the varicella, pneumococcal, and influenza vaccinations, are important adjuncts. (See section below titled Immunization Against Infectious Diseases.)

Treatment

A. Fever in an Intensive Care Unit Patient

Unless the patient has a central neurologic injury with elevated intracranial pressure or has a temperature higher than 41°C, there is less physiologic need to maintain euthermia. Empiric broad-spectrum antibiotics (see Table 30–5)

are recommended for neutropenic and other immunocompromised patients and in patients who are clinically unstable.

B. Catheter-Associated Infections

Factors that inform treatment decisions include the type of catheter, the causative pathogen, the availability of alternate catheter access sites, the need for ongoing intravascular access, and the severity of disease.

In general, catheters should be removed if there is purulence at the exit site; if the organism is *S aureus*, gram-negative rods, or *Candida* species; if there is persistent bacteremia (more than 48 hours while receiving antibiotics); or if complications, such as septic thrombophlebitis, endocarditis, or other metastatic disease, exist. Central venous catheters may be exchanged over a guidewire provided there is no erythema or purulence at the exit site and the patient does not appear to be septic. Methicillin-resistant, coagulase-negative staphylococci are the most common pathogens; thus, empiric therapy with vancomycin, 15 mg/kg/dose intravenously twice daily, should be given assuming normal kidney function. Empiric gram-negative coverage should be used in patients who are immunocompromised or who are critically ill (see Table 30–5).

Antibiotic treatment duration depends on the pathogen and the extent of disease. For uncomplicated bacteremia, 5–7 days of therapy is usually sufficient for coagulase-negative staphylococci, even if the original catheter is retained. Fourteen days of therapy are generally recommended for uncomplicated bacteremia caused by gram-negative rods, *Candida* species, and *S aureus*. **Antibiotic lock therapy** involves the instillation of supratherapeutic concentrations of antibiotics with heparin in the lumen of catheters. The purpose is to achieve adequate concentrations of antibiotics to kill microbes in the biofilm. Antibiotic lock therapy can be used for catheter-related bloodstream infections caused by both gram-positive and gram-negative bacterial pathogens and when the catheter is being retained in a salvage situation.

► When to Refer

- Any patient with multidrug-resistant infection.
- Any patient with fungemia, *S aureus* bacteremia, or persistent bacteremia of any organism.
- Patients whose catheters cannot be removed.
- Patients with multisite infections.
- Patients with impaired or fluctuating kidney function for assistance with dosing of antimicrobials.
- Patients with refractory or recurrent *C difficile* colitis.

Bupha-Intr O et al. Efficacy of early oral switch with β-lactams for low-risk *Staphylococcus aureus* bacteremia. *Antimicrob Agents Chemother* 2020;64:e02345-19. [PMID: 32015029]
DeFilipp Z et al. Drug-resistant *E. coli* bacteremia transmitted by fecal microbiota transplant. *N Engl J Med*. 2019;381:2043. [PMID: 31665575]

Table 30–1. Typical cerebrospinal fluid findings in various central nervous system diseases (listed in alphabetical order after Normal).

Diagnosis	Cells/mcL	Glucose (mg/dL)	Protein (mg/dL)	Opening Pressure
Normal	0–5 lymphocytes	45–85 ¹	15–45	70–180 mm H ₂ O
Aseptic meningitis, viral meningitis, or meningoencephalitis ²	25–2000 (0.025–2.0 × 10 ⁹ /L), mostly lymphocytes ³	Normal or low	High (> 50)	Slightly elevated
Granulomatous meningitis (mycobacterial, fungal) ³	100–1000 (0.1–1.0 × 10 ⁹ /L), mostly lymphocytes ³	Low (< 45)	High (> 50)	Moderately elevated
"Neighborhood reaction" ⁴	Variably increased	Normal	Normal or high	Variable
Purulent meningitis (bacterial) ⁵ community-acquired	200–20,000 (0.2–20 × 10 ⁹ /L) polymorphonuclear neutrophils	Low (< 45)	High (> 50)	Markedly elevated
Spirochetal meningitis	100–1000 (0.1–1.0 × 10 ⁹ /L), mostly lymphocytes ³	Normal	High (> 50)	Normal to slightly elevated

¹Cerebrospinal fluid glucose must be considered in relation to blood glucose level. Normally, cerebrospinal fluid glucose is 20–30 mg/dL lower than blood glucose, or 50–70% of the normal value of blood glucose.

²Viral isolation from cerebrospinal fluid early; antibody titer rise in paired specimens of serum; polymerase chain reaction for herpesvirus.

³Polymorphonuclear neutrophils may predominate early.

⁴May occur in mastoiditis, brain abscess, epidural abscess, sinusitis, septic thrombus, brain tumor. Cerebrospinal fluid culture results usually negative.

⁵Organisms in smear or culture of cerebrospinal fluid; counterimmunolectrophoresis or latex agglutination may be diagnostic.

- Harris PNA et al; MERINO Trial Investigators and the Australasian Society for Infectious Disease Clinical Research Network (ASID-CRN). Effect of piperacillin-tazobactam vs meropenem on 30-day mortality for patients with *E coli* or *Klebsiella pneumoniae* bloodstream infection and ceftriaxone resistance: a randomized clinical trial. JAMA. 2018;320:984. [PMID: 30208454]
- McDonald LC et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis. 2018;66:e1. [PMID: 29462280]
- Ostrowsky B et al. *Candida auris* isolates resistant to three classes of antifungal medications—New York, 2019. MMWR Morb Mortal Wkly Rep. 2020;69:6. [PMID: 31917780]
- Radonovich LJ Jr et al; ResPECT Investigators. N95 respirators vs medical masks for preventing influenza among health care personnel: a randomized clinical trial. JAMA. 2019;322:824. [PMID: 31479137]

INFECTIONS OF THE CENTRAL NERVOUS SYSTEM



- ▶ CNS infection is a medical emergency.
- ▶ Symptoms and signs common to all CNS infections include headache, fever, sensorial disturbances, neck and back stiffness, positive Kernig and Brudzinski signs, and cerebrospinal fluid abnormalities.

► General Considerations

Infections of the CNS can be caused by almost any infectious agent, including bacteria, mycobacteria, fungi, spirochetes, protozoa, helminths, and viruses.

► Etiologic Classification

CNS infections can be divided into several categories that usually can be readily distinguished from each other by cerebrospinal fluid examination as the first step toward etiologic diagnosis (Table 30–1).

A. Purulent Meningitis

Patients with bacterial meningitis usually seek medical attention within hours or 1–2 days after onset of symptoms. The organisms responsible depend primarily on the age of the patient as summarized in Table 30–2. The diagnosis is usually based on the Gram-stained smear (positive in 60–90%) or culture (positive in over 90%) of the cerebrospinal fluid.

B. Chronic Meningitis

The presentation of chronic meningitis is less acute than purulent meningitis. Patients with chronic meningitis usually have a history of symptoms lasting weeks to months. The most common pathogens are *Mycobacterium tuberculosis*, atypical mycobacteria, fungi (*Cryptococcus*, *Coccidioides*, *Histoplasma*), and spirochetes (*Treponema pallidum* and *Borrelia burgdorferi*). The diagnosis is made by culture or in some cases by serologic tests (cryptococcosis, coccidioidomycosis, syphilis, Lyme disease).

C. Aseptic Meningitis

Aseptic meningitis—a much more benign and self-limited syndrome than purulent meningitis—is caused principally by viruses, especially herpes simplex virus and the enterovirus group (including coxsackieviruses and echoviruses). Infectious mononucleosis may be accompanied by aseptic meningitis. Leptospiral infection is also usually placed in

Table 30–2. Initial antimicrobial therapy for purulent meningitis of unknown cause.

Population	Usual Microorganisms	Standard Therapy
18–50 years	<i>Streptococcus pneumoniae</i> , <i>Neisseria meningitidis</i>	Vancomycin ¹ plus ceftriaxone ²
Over 50 years	<i>S pneumoniae</i> , <i>N meningitidis</i> , <i>Listeria monocytogenes</i> , gram-negative bacilli, group B streptococcus	Vancomycin ¹ plus ampicillin, ³ plus ceftriaxone ²
Impaired cellular immunity	<i>L monocytogenes</i> , gram-negative bacilli, <i>S pneumoniae</i>	Vancomycin ¹ plus ampicillin, ³ plus ceftazidime ⁴
Postsurgical or posttraumatic	<i>Staphylococcus aureus</i> , <i>S pneumoniae</i> , aerobic gram-negative bacilli, coagulase-negative staphylococci, ⁵ diphtheroids (eg, <i>Propionibacterium acnes</i>) ⁵ (uncommon)	Vancomycin ¹ plus ceftazidime ⁴

¹Given to cover highly penicillin- or cephalosporin-resistant pneumococci. The dose of vancomycin is 15 mg/kg/dose intravenously every 8 hours. A target area under the curve (AUC) between 400 and 600 mg*hour/L is suggested for treatment of confirmed methicillin-resistant *Staphylococcus aureus* (MRSA). Should be stopped if the causative organism is susceptible to ceftriaxone.

²Ceftriaxone can often be used safely in most patients with a history of penicillin allergy (aztreonam can be considered for empiric coverage of gram-negative bacilli in patients with type 1 IgE-mediated penicillin and cephalosporin allergy). The usual dose of ceftriaxone is 2 g intravenously every 12 hours. If the organism is susceptible, penicillin 3–4 million units intravenously every 4 hours is given.

³In severely ill patients, ampicillin is used when *L monocytogenes* infection is a consideration. For confirmed infection due to *L monocytogenes*, gentamicin is sometimes added to ampicillin. (For patients with type 1 IgE-mediated penicillin allergy, trimethoprim-sulfamethoxazole [TMP-SMZ] in a dosage of 15–20 mg/kg/day of TMP in 3 or 4 divided doses can be considered.) The dose of ampicillin is 2 g intravenously every 4 hours with normal kidney function.

⁴Cefepime is given in a dose of 3 g intravenously every 8 hours.

⁵Primarily associated with presence of hardware.

the aseptic group because of the lymphocytic cellular response and its relatively benign course. This type of meningitis also occurs during secondary syphilis and disseminated Lyme disease. Prior to the routine administration of measles-mumps-rubella (MMR) vaccines, mumps was the most common cause of viral meningitis. Drug-induced aseptic meningitis has been reported with nonsteroidal anti-inflammatory drugs, sulfonamides, and certain monoclonal antibodies.

D. Encephalitis

Encephalitis (due to herpesviruses, arboviruses, rabies virus, flaviviruses [West Nile encephalitis, Japanese encephalitis], and many others) produces disturbances of the sensorium, seizures, and many other manifestations. Patients are more ill than those with aseptic meningitis. Cerebrospinal fluid may be entirely normal or may show some lymphocytes and, in some instances (eg, herpes simplex), red cells as well. Influenza has been associated with encephalitis, but the relationship is not clear. An autoimmune form of encephalitis associated with N-methyl-D-aspartate receptor antibodies should be suspected in younger patients with encephalitis and associated seizures, movement disorders, and psychosis.

E. Partially Treated Bacterial Meningitis

Previous effective antibiotic therapy given for 12–24 hours will decrease the rate of positive cerebrospinal fluid Gram stain results by 20% and culture by 30–40% but will have little effect on cell count, protein, or glucose. Occasionally, previous antibiotic therapy will change a predominantly polymorphonuclear response to a lymphocytic pleocytosis,

and some of the cerebrospinal fluid findings may be similar to those seen in aseptic meningitis.

F. Neighborhood Reaction

As noted in Table 30–1, this term denotes a purulent infectious process in close proximity to the CNS that spills some of the products of the inflammatory process—white blood cells or protein—into the cerebrospinal fluid. Such an infection might be a brain abscess, osteomyelitis of the vertebrae, epidural abscess, subdural empyema, or bacterial sinusitis or mastoiditis.

G. Noninfectious Meningeal Irritation

Carcinomatous meningitis, sarcoidosis, systemic lupus erythematosus, chemical meningitis, and certain medications—nonsteroidal anti-inflammatory drugs, OKT3, TMP-SMZ, and others—can also produce symptoms and signs of meningeal irritation with associated cerebrospinal fluid pleocytosis, increased protein, and low or normal glucose. Meningismus with normal cerebrospinal fluid findings occurs in the presence of other infections such as pneumonia and shigellosis.

H. Brain Abscess

Brain abscess presents as a space-occupying lesion; symptoms may include vomiting, fever, change of mental status, or focal neurologic manifestations. When brain abscess is suspected, a CT scan should be performed. If positive, lumbar puncture should *not* be performed since results rarely provide clinically useful information and herniation can occur. The bacteriology of brain abscess is usually polymicrobial and includes *S aureus*, gram-negative bacilli,

streptococci, and mouth anaerobes (including anaerobic streptococci and *Prevotella* species).

I. Health Care–Associated Meningitis

This infection may arise as a result of invasive neurosurgical procedures (eg, craniotomy, internal or external ventricular catheters, external lumbar catheters), complicated head trauma, or hospital-acquired bloodstream infections. Outbreaks have been associated with contaminated epidural or paraspinal corticosteroid injections. In general, the microbiology is distinct from community-acquired meningitis, with gram-negative organisms (eg, *Pseudomonas*), *S aureus*, and coagulase-negative staphylococci and, in the outbreaks associated with contaminated corticosteroids, mold and fungi (*Exserohilum rostratum* and *Aspergillus fumigatus*) playing a larger role.

► Clinical Findings

A. Symptoms and Signs

The classic triad of fever, stiff neck, and altered mental status has a low sensitivity (44%) for bacterial meningitis. However, nearly all patients with bacterial meningitis have at least two of the following symptoms—fever, headache, stiff neck, or altered mental status.

B. Laboratory Tests

Evaluation of a patient with suspected meningitis includes a blood count, blood culture, lumbar puncture followed by careful study and culture of the cerebrospinal fluid, and a chest film. The fluid must be examined for cell count, glucose, and protein, and a smear stained for bacteria (and acid-fast organisms when appropriate) and cultured for pyogenic organisms and for mycobacteria and fungi when indicated. Latex agglutination tests can detect antigens of encapsulated organisms (*S pneumoniae*, *H influenzae*, *N meningitidis*, and *Cryptococcus neoformans*) but are rarely used except for detection of *Cryptococcus* or in partially treated patients. Polymerase chain reaction (PCR) testing of cerebrospinal fluid has been used to detect bacteria (*S pneumoniae*, *H influenzae*, *N meningitidis*, *M tuberculosis*, *B burgdorferi*, and *Tropheryma whipplei*) and viruses (herpes simplex, varicella-zoster, CMV, Epstein-Barr virus, and enteroviruses) in patients with meningitis. The greatest experience is with PCR for herpes simplex, varicella-zoster, and JC virus. These tests are very sensitive (greater than 95%) and specific. In addition to its use in meningitis, molecular methods such as PCR and next-generation sequencing are being used increasingly for the diagnosis of encephalitis, transverse myelitis, and brain abscess. In general, molecular diagnostic tests may provide a more sensitive and rapid alternative to traditional culture and serology methods. However, it is difficult to ascertain the true sensitivity of many molecular tests for CNS infections given the absence of a gold standard. In some cases, tests to detect several organisms may not be any more sensitive than culture (or serology), but the real value is the rapidity with which results are available, ie, hours compared with days or weeks.

C. Lumbar Puncture and Imaging

Since performing a lumbar puncture in the presence of a space-occupying lesion (brain abscess, subdural hematoma, subdural empyema, necrotic temporal lobe from herpes encephalitis) may result in brainstem herniation, *a CT scan is performed prior to lumbar puncture if a space-occupying lesion is suspected on the basis of papilledema, seizures, or focal neurologic findings*. Other indications for CT scan are an immunocompromised patient or moderately to severely impaired level of consciousness. If delays are encountered in obtaining a CT scan and bacterial meningitis is suspected, blood cultures should be drawn and antibiotics and corticosteroids administered even before cerebrospinal fluid is obtained for culture to avoid delay in treatment (Table 30-1). *Antibiotics given within 4 hours before obtaining cerebrospinal fluid probably do not affect culture results*. MRI with contrast of the epidural injection site and surrounding areas is recommended (sometimes repeatedly) for those with symptoms following a possibly contaminated corticosteroid injection to exclude epidural abscess, phlegmon, vertebral osteomyelitis, discitis, or arachnoiditis.

► Treatment

Although it is difficult to prove with existing clinical data that early antibiotic therapy improves outcome in bacterial meningitis, prompt therapy is still recommended. In purulent meningitis, the identity of the causative microorganism may remain unknown or doubtful for a few days and initial antibiotic treatment as set forth in Table 30-2 should be directed against the microorganisms most common for each age group.

The duration of therapy for bacterial meningitis varies depending on the etiologic agent: *H influenzae*, 7 days; *N meningitidis*, 3–7 days; *S pneumoniae*, 10–14 days; *L monocytogenes*, 14–21 days; and gram-negative bacilli, 21 days.

For adults with pneumococcal meningitis, dexamethasone 10 mg administered intravenously 15–20 minutes before or simultaneously with the first dose of antibiotics and continued every 6 hours for 4 days decreases morbidity and mortality. Patients most likely to benefit from corticosteroids are those infected with gram-positive organisms (*S pneumoniae* or *S suis*), and those who are HIV negative. It is unknown whether patients with meningitis due to *N meningitidis* and other bacterial pathogens benefit from the use of adjunctive corticosteroids. Increased intracranial pressure due to brain edema often requires therapeutic attention. Hyperventilation, mannitol (25–50 g intravenously as a bolus), and even drainage of cerebrospinal fluid by repeated lumbar punctures or by placement of intraventricular catheters have been used to control cerebral edema and increased intracranial pressure. Dexamethasone (4 mg intravenously every 4–6 hours) may also decrease cerebral edema.

Therapy of brain abscess consists of drainage (excision or aspiration) in addition to 3–4 weeks of systemic antibiotics directed against organisms isolated. An empiric regimen often includes metronidazole, 500 mg intravenously or orally every 8 hours, plus ceftriaxone, 2 g intravenously every 12 hours, with or without vancomycin, 10–15 mg/kg/dose

intravenously every 12 hours. Vancomycin trough serum levels should be greater than 15 mcg/mL in such patients; however, achievement of an area under the curve/minimal inhibitory concentration (AUC/MIC) ratio of 400–600 is a better predictor of outcome and should be used in confirmed MRSA abscesses. In cases where abscesses are smaller than 2 cm, where there are multiple abscesses that cannot be drained, or if an abscess is located in an area where significant neurologic sequelae would result from drainage, antibiotics for 6–8 weeks can be used without drainage.

In addition to antibiotics, in cases of health care-associated meningitis associated with an external intraventricular catheter, the probability of cure is increased if the catheter is removed. In infections associated with internal ventricular catheters, removal of the internal components and insertion of an external drain is recommended. After collecting cerebrospinal fluid, epidural aspirate, or other specimens for culture, routine empiric treatment for other pathogens (as above) is recommended until the specific cause of the patient's CNS or parameningeal infection has been identified. In addition, early consultation with a neurosurgeon is recommended for those found to have an epidural abscess, phlegmon, vertebral osteomyelitis, discitis, or arachnoiditis to discuss possible surgical management (eg, debridement).

Therapy of other types of meningitis is discussed elsewhere in this book (fungal meningitis, Chapter 36; syphilis and Lyme borreliosis, Chapter 34; tuberculous meningitis, Chapter 33; herpes encephalitis, Chapter 32).

► When to Refer

- Patients with acute meningitis, particularly if culture negative or atypical (eg, fungi, syphilis, Lyme disease, *M tuberculosis*), or if hospital acquired, associated with an intraventricular catheter, or if the patient is immunosuppressed.
- Patients with chronic meningitis.
- All patients with brain abscesses and encephalitis.
- Patients with suspected hospital-acquired meningitis (eg, in patients who have undergone recent neurosurgery or epidural or paraspinal corticosteroid injection).
- Patients with recurrent meningitis.

► When to Admit

- Patients with suspected acute meningitis, encephalitis, and brain or paraspinal abscess should be admitted for urgent evaluation and treatment.
- There is less urgency to admit patients with chronic meningitis; these patients may be admitted to expedite diagnostic procedures and coordinate care, particularly if no diagnosis has been made in the outpatient setting.

Fitzgerald D et al. Invasive pneumococcal and meningococcal disease. Infect Dis Clin North Am. 2019;33:1125. [PMID: 31668194]

Tunkel AR et al. 2017 Infectious Diseases Society of America's clinical practice guidelines for healthcare-associated ventriculitis and meningitis. Clin Infect Dis. 2017;64:e34. [PMID: 28203777]

Vestergaard HH et al. Normocellular community-acquired bacterial meningitis in adults: a nationwide population-based case series. Ann Emerg Med. 2021;77:11. [PMID: 32747082]
Wilson MR et al. Clinical metagenomic sequencing for diagnosis of meningitis and encephalitis. N Engl J Med. 2019;380(24):2327. [PMID: 31189036]

ANIMAL & HUMAN BITE WOUNDS



ESSENTIALS OF DIAGNOSIS

- ▶ Cat and human bites have higher rates of infection than dog bites.
- ▶ Hand bites are particularly concerning for the possibility of closed-space infection.
- ▶ Antibiotic prophylaxis indicated for noninfected bites of the hand and hospitalization required for infected hand bites.
- ▶ All infected wounds need to be cultured to direct therapy.

► General Considerations

About 1000 dog bite injuries require emergency department attention each day in the United States, most often in urban areas. Dog bites occur most commonly in the summer months. Biting animals are usually known by their victims, and most biting incidents are provoked (ie, bites occur while playing with the animal or after surprising the animal while eating or waking it abruptly from sleep). Failure to elicit a history of provocation is important, because *an unprovoked attack raises the possibility of rabies*. Human bites are usually inflicted by children while playing or fighting; in adults, bites are associated with alcohol use and closed-fist injuries that occur during fights.

The animal inflicting the bite, the location of the bite, and the type of injury inflicted are all important determinants of whether they become infected. Cat bites are more likely to become infected than human bites—between 30% and 50% of all cat bites become infected. Infections following human bites are variable. Bites inflicted by children rarely become infected because they are superficial, and bites by adults become infected in 15–30% of cases, with a particularly high rate of infection in closed-fist injuries. Dog bites, for unclear reasons, become infected only 5% of the time. Bites of the head, face, and neck are less likely to become infected than bites on the extremities. “Through and through” bites (eg, involving the mucosa and the skin) have an infection rate similar to closed-fist injuries. Puncture wounds become infected more frequently than lacerations, probably because the latter are easier to irrigate and debride.

The bacteriology of bite infections is polymicrobial. Following dog and cat bites, over 50% of infections are caused by aerobes and anaerobes and 36% are due to aerobes alone. Pure anaerobic infections are rare. *Pasteurella*

species are the single most common isolate (75% of infections caused by cat bites and 50% of infections caused by dog bites). Other common aerobic isolates include streptococci, staphylococci, *Moraxella*, and *Neisseria*; the most common anaerobes are *Fusobacterium*, *Bacteroides*, *Porphyromonas*, and *Prevotella*. The median number of isolates following human bites is four (three aerobes and one anaerobe). Like dog and cat bites, infections caused by most human bites are a mixture of aerobes and anaerobes (54%) or are due to aerobes alone (44%). Streptococci and *S aureus* are the most common aerobes. *Eikenella corrodens* (found in up to 30% of patients), *Prevotella*, and *Fusobacterium* are the most common anaerobes. Although the organisms noted are the most common, innumerable others have been isolated—including *Capnocytophaga* (dog and cat), *Pseudomonas*, and *Haemophilus*—emphasizing the point that *all infected bites should be cultured* to define the microbiology.

HIV can be transmitted from bites (either from biting or receiving a bite from an HIV-infected patient) but has rarely been reported.

Treatment

A. Local Care

Vigorous cleansing and irrigation of the wound as well as debridement of necrotic material are the most important factors in decreasing the incidence of infections. Radiographs should be obtained to look for fractures and the presence of foreign bodies. Careful examination to assess the extent of the injury (tendon laceration, joint space penetration) is critical to appropriate care.

B. Suturing

If wounds require closure for cosmetic or mechanical reasons, suturing can be done. However, *one should never suture an infected wound*, and wounds of the hand should generally not be sutured since a closed-space infection of the hand can result in loss of function.

C. Prophylactic Antibiotics

Prophylaxis is indicated in high-risk bites and in high-risk patients. **Cat bites in any location and hand bites by any animal, including humans, should receive prophylaxis.** Individuals with certain comorbidities (diabetes, liver disease) are at increased risk for severe complications and should receive prophylaxis even for low-risk bites, as should patients without functional spleens who are at increased risk for overwhelming sepsis (primarily with *Capnocytophaga* species). Amoxicillin-clavulanate (Augmentin) 500 mg orally three times daily for 5–7 days is the regimen of choice. For patients with serious allergy to penicillin, a combination of clindamycin 300 mg orally three times daily together with one of the following is recommended for 5–7 days: doxycycline 100 mg orally twice daily, or double-strength TMP-SMZ orally twice daily, or a fluoroquinolone (ciprofloxacin 500 mg orally

twice daily or levofloxacin 500–750 mg orally once daily). Moxifloxacin, a fluoroquinolone with good aerobic and anaerobic activity, may be suitable as monotherapy at 400 mg orally once daily for 5–7 days. Agents such as dicloxacillin, cephalaxin, macrolides, and clindamycin should not be used alone because they lack activity against *Pasteurella* species. TMP-SMZ has poor activity against anaerobes and should only be used in combination with clindamycin.

Because the risk of HIV transmission is so low following a bite, routine postexposure prophylaxis is *not* recommended. Each case should be evaluated individually and consideration for prophylaxis should be given to those who present within 72 hours of the incident, the source is known to be HIV infected, and the exposure is high risk.

D. Antibiotics for Documented Infection

For wounds that are infected, antibiotics are clearly indicated. How they are given (orally or intravenously) and the need for hospitalization are individualized clinical decisions. The most commonly encountered pathogens require treatment with ampicillin-sulbactam (Unasyn), 1.5–3.0 g intravenously every 6–8 hours; or amoxicillin-clavulanate (Augmentin), 500 mg orally three times daily; or ertapenem, 1 g intravenously daily. For the patient with severe penicillin allergy, a combination of clindamycin, 600–900 mg intravenously every 8 hours, plus a fluoroquinolone (ciprofloxacin, 400 mg intravenously every 12 hours; levofloxacin, 500–750 mg intravenously once daily) is indicated. Duration of therapy is usually 2–3 weeks unless complications such as septic arthritis or osteomyelitis are present; if these complications are present, therapy should be extended to 4 and 6 weeks, respectively.

E. Tetanus and Rabies

All patients must be evaluated for the need for tetanus (see Chapter 33) and rabies (see Chapter 32) prophylaxis.

When to Refer

- If septic arthritis or osteomyelitis is suspected.
- For exposure to bites by dogs, cats, reptiles, amphibians, and rodents.
- When rabies is a possibility.

When to Admit

- Patients with infected hand bites.
- Deep bites, particularly if over joints.

Dhillon J et al. Scoping decades of dog evidence: a scoping review of dog bite-related sequelae. *Can J Public Health.* 2019;110:364. [PMID: 30378009]

Greene SE et al. Infectious complications of bite injuries. *Infect Dis Clin North Am.* 2021;35:219. [PMID: 33494873]

Kheiran A et al. Cat bite: an injury not to underestimate. *J Plast Surg Hand Surg.* 2019;53:341. [PMID: 31287352]

SEXUALLY TRANSMITTED DISEASES



ESSENTIALS OF DIAGNOSIS

- ▶ All sexually transmitted diseases (STDs) have subclinical or latent periods, and patients may be asymptomatic.
- ▶ Simultaneous infection with several organisms is common.
- ▶ All patients who seek STD testing should be screened for syphilis and HIV.
- ▶ Partner notification and treatment are important to prevent further transmission and reinfection of the index case.

► General Considerations

The most common STDs are gonorrhea,* syphilis,* human papillomavirus (HPV)-associated condyloma acuminatum, chlamydial genital infections,* herpesvirus genital infections, trichomonas vaginitis, chancroid,* granuloma inguinale, scabies, louse infestation, and bacterial vaginosis (among women who have sex with women). However, shigellosis*; hepatitis A, B, and C*; amebiasis; giardiasis*; cryptosporidiosis*; salmonellosis*; and campylobacteriosis may also be transmitted by sexual (oral-anal) contact, especially in men who have sex with men. Ebola virus and Zika virus have both been associated with sexual transmission. Both homosexual and heterosexual contact are risk factors for the transmission of HIV (see Chapter 31). All STDs have *subclinical* or *latent phases* that play an important role in long-term persistence of the infection or in its transmission from infected (but largely asymptomatic) persons to other contacts. Simultaneous infection by several different agents is common.

Infections typically present in one of several ways, each of which has a defined differential diagnosis, which should prompt appropriate diagnostic tests.

A. Genital Ulcers

Common etiologies include herpes simplex virus, primary syphilis, and chancroid. Other possibilities include lymphogranuloma venereum (see Chapter 33), granuloma inguinale caused by *Klebsiella granulomatis* (see Chapter 33), as well as lesions caused by infection with Epstein-Barr virus and HIV. Noninfectious causes are Behçet disease (see Chapter 20), neoplasm, trauma, drugs, and irritants.

B. Urethritis With or Without Urethral Discharge

The most common infections causing urethral discharge are *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. *N gonorrhoeae* and *C trachomatis* are also frequent causes of prostatitis among sexually active men. Other sexually transmitted infections that can cause urethritis include *Mycoplasma genitalium* and, less commonly, *Ureaplasma*

urealyticum and *Trichomonas vaginalis*. Noninfectious causes of urethritis include reactive arthritis with associated urethritis.

C. Vaginal Discharge

Common causes of vaginitis are bacterial vaginosis (caused by overgrowth of anaerobes such as *Gardnerella vaginalis*), candidiasis, and *T vaginalis* (see Chapter 18). Less common infectious causes of vaginitis include HPV-associated condylomata acuminata and group A streptococcus. Noninfectious causes are physiologic changes related to the menstrual cycle, irritants, and lichen planus. Even though *N gonorrhoeae* and *C trachomatis* are frequent causes of cervicitis, they rarely produce vaginal discharge.

► Screening & Prevention

All persons who seek STD testing should undergo routine screening for HIV infection, using rapid HIV testing (if patients may not follow up for results obtained by standard methods) or nucleic acid amplification followed by confirmatory serology (if primary HIV infection may be a possibility) as indicated. Most algorithms now start with an antigen/antibody combination HIV-1/2 immunoassay with a confirmatory HIV-1/HIV-2 antibody differentiation immunoassay. Patients in whom certain STDs have been diagnosed and treated (chlamydia or gonorrhea, and trichomonas in women) are at a high risk for reinfection and should be encouraged to be rescreened for STDs at 3 months following the initial STD diagnosis.

Asymptomatic patients often request STD screening at the time of initiating a new sexual relationship. Routine HIV testing and hepatitis B serology testing should be offered to all such patients. In sexually active women who have not been recently screened, cervical Papanicolaou testing and nucleic acid amplification testing of a urine specimen for gonorrhea and chlamydia are recommended. Among men who have sex with men, additional screening is recommended for syphilis; hepatitis A; urethral, pharyngeal, and rectal gonorrhea; as well as urethral and rectal chlamydia. Nucleic acid amplification testing is recommended for gonorrhea or chlamydia. There are no recommendations to screen heterosexual men for urethral chlamydia, but this could be considered in STD clinics, adolescent clinics, or correctional facilities. The periodicity of screening thereafter depends on sexual risk, but most screening should be offered at least annually to sexually active adults (particularly to those 25 years old and under). Clinicians should also evaluate transgender men and women for STD screening, based on current anatomy and behaviors practiced. If not immune, hepatitis B vaccination is recommended for all sexually active adults, and hepatitis A vaccination in men who have sex with men. Persons between the ages of 9 and 26 should be routinely offered vaccination against HPV (9-valent).

The risk of developing an STD following a sexual assault is difficult to accurately ascertain given high rates of baseline infections and poor follow-up. Victims of assault have a high baseline rate of infection (*N gonorrhoeae*, 6%; *C trachomatis*, 10%; *T vaginalis*, 15%; and bacterial

*Reportable to public health authorities.

vaginosis, 34%), and the risk of acquiring infection as a result of the assault is significant but is often lower than the preexisting rate (*N gonorrhoeae*, 6–12%; *C trachomatis*, 4–17%; *T vaginalis*, 12%; syphilis, 0.5–3%; and bacterial vaginosis, 19%). Victims should be evaluated within 24 hours after the assault, and nucleic acid amplification tests for *N gonorrhoeae* and *C trachomatis* should be performed. Vaginal secretions are obtained for *Trichomonas* wet mount and culture, or point-of-care testing. If a discharge is present, if there is itching, or if secretions are malodorous, a wet mount should be examined for *Candida* and bacterial vaginosis. In addition, a blood sample should be obtained for immediate serologic testing for syphilis, hepatitis B, and HIV. Follow-up examination for STDs should be repeated within 1–2 weeks, since concentrations of infecting organisms may not have been sufficient to produce a positive test at the time of initial examination. If prophylactic treatment was given (may include postexposure hepatitis B vaccination without hepatitis B immune globulin; treatment for chlamydial, gonorreal, or trichomonal infection; and emergency contraception), tests should be repeated only if the victim has symptoms. If prophylaxis was not administered, the individual should be seen in 1 week so that any positive tests can be treated. Follow-up serologic testing for syphilis and HIV infection should be performed in 6, 12, and 24 weeks if the initial tests are negative. The usefulness of presumptive therapy is controversial, with some feeling that all patients should receive it and others that it should be limited to those in whom follow-up cannot be ensured or to patients who request it.

Although seroconversion to HIV has been reported following sexual assault when this was the only known risk, this risk is believed to be low. The likelihood of HIV transmission from vaginal or anal receptive intercourse when the source is known to be HIV positive is 1 per 1000 and 5 per 1000, respectively. Although prophylactic antiretroviral therapy has not been studied in this setting, the Department of Health and Human Services recommends the prompt institution of *postexposure prophylaxis with antiretroviral therapy if the person seeks care within 72 hours of the assault*, the source is known to be HIV positive, and the exposure presents a substantial risk of transmission.

In addition to screening asymptomatic patients with STDs, other strategies for preventing further transmission include evaluating sex partners and administering preexposure vaccination of preventable STDs to individuals at risk; other strategies include the consistent use of male and female condoms and male circumcision. Adult male circumcision has been shown to decrease the transmission of HIV by 50%, and of herpes simplex virus and HPV by 30% in heterosexual couples in sub-Saharan Africa. For each patient, there are one or more sexual contacts who require diagnosis and treatment. Prompt treatment of contacts by giving antibiotics to the index case to distribute to all sexual contacts (**patient-delivered therapy**) is an important strategy for preventing further transmission and to prevent reinfection of the index case.

Note that vaginal spermicides and condoms containing nonoxynol-9 provide no additional protection against STDs. Early initiation of antiretroviral therapy in

HIV-infected individuals can prevent HIV acquisition in an uninfected sex partner. Also, preexposure prophylaxis with a once-daily pill containing emtricitabine plus tenofovir disoproxil fumarate (TDF) has been shown to be effective in preventing HIV infection among high-risk men who have sex with men, heterosexual women and men, transgender women, and persons who inject drugs.

► When to Refer

- Patients with a new diagnosis of HIV.
- Patients with persistent, refractory, or recurrent STDs, particularly when drug resistance is suspected.

Chou R et al. Preexposure prophylaxis for the prevention of HIV infection: evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2019;321:2214. [PMID: 31184746]

MacGowan RJ et al. Effect of internet-distributed HIV self-tests on HIV diagnosis and behavioral outcomes in men who have sex with men: a randomized clinical trial. *JAMA Intern Med*. 2020;180:117. [PMID: 31738378]

Price JC et al. Sexually acquired hepatitis C infection in HIV-uninfected men who have sex with men using pre-exposure prophylaxis against HIV. *J Infect Dis*. 2019;219:1373. [PMID: 30462305]

US Preventive Services Task Force; Krist AH et al. Behavioral counseling interventions to prevent sexually transmitted infections: US Preventive Services Task Force recommendation statement. *JAMA*. 2020;324:674. [PMID: 32809008]

INFECTIONS IN PERSONS WHO INJECT DRUGS

ESSENTIALS OF DIAGNOSIS

- ▶ Common infections that occur with greater frequency in persons who inject drugs include:
 - Skin infections, aspiration pneumonia, tuberculosis.
 - Hepatitis A, B, C, D; STDs; HIV/AIDS.
 - Pulmonary septic emboli, infective endocarditis.
 - Osteomyelitis and septic arthritis.

► General Considerations

There is a high incidence of infection among persons with opioid use disorder, particularly among people who inject drugs. Increased risk of infection is likely associated with poor hygiene and colonization with potentially pathogenic organisms, contamination of drugs and equipment, increased sexual risk behaviors, and impaired immune defenses. The use of parenterally administered recreational drugs has increased enormously in recent years, fueled in part by an epidemic of prescription opioid misuse and abuse. More than 2 million persons in North America are estimated to have used injection drugs in the past year.

Skin infections are associated with poor hygiene and use of nonsterile technique when injecting drugs. *S aureus*

(including community-acquired methicillin-resistant strains) and oral flora (*streptococci*, *Eikenella*, *Fusobacterium*, *Pestostreptococcus*) are the most common organisms, with enteric gram-negatives generally more likely seen in those who inject into the groin. Cellulitis and subcutaneous abscesses occur most commonly, particularly in association with subcutaneous (“skin-popping”) or intramuscular injections and the use of cocaine and heroin mixtures (probably due to ischemia). Myositis, clostridial myonecrosis, and necrotizing fasciitis occur infrequently but are life-threatening. Wound botulism in association with black tar heroin occurs sporadically but often in clusters.

Aspiration pneumonia and its complications (lung abscess, empyema, brain abscess) result from altered consciousness associated with drug use. Mixed aerobic and anaerobic mouth flora are usually involved.

Tuberculosis also occurs in persons who use drugs, and infection with HIV has fostered the spread of tuberculosis in this population. Morbidity and mortality rates are increased in HIV-infected individuals with tuberculosis. Classic radiographic findings are often absent; tuberculosis is suspected in any patient with infiltrates who does not respond to antibiotics.

Hepatitis is very common among persons who inject drugs and is transmissible both by the parenteral (hepatitis B, C, and D) and by the fecal-oral route (hepatitis A). Multiple episodes of hepatitis with different agents can occur. Hepatitis C has also been associated with non-injection heroin use as well as intranasal use of other drugs, likely secondary to blood on shared straws.

Pulmonary septic emboli may originate from venous thrombi or right-sided endocarditis.

STDs are not directly related to drug use, but the practice of exchanging sex for drugs has resulted in an increased frequency of STDs. Syphilis, gonorrhea, and chancroid are the most common.

HIV/AIDS has a high incidence among persons who inject drugs and their sexual contacts and among the offspring of infected women (see Chapter 31).

Infective endocarditis in persons who inject drugs is most commonly caused by *S aureus*, *Candida* (usually *C albicans* or *C parapsilosis*), *Enterococcus faecalis*, other streptococci, and gram-negative bacteria (especially *Pseudomonas* and *Serratia marcescens*). See Chapter 33.

Other vascular infections include septic thrombophlebitis and mycotic aneurysms. Mycotic aneurysms resulting from direct trauma to a vessel with secondary infection most commonly occur in femoral arteries and less commonly in arteries of the neck. Aneurysms resulting from hematogenous spread of organisms frequently involve intracerebral vessels and thus are seen in association with endocarditis.

Osteomyelitis and **septic arthritis** involving vertebral bodies, sternoclavicular joints, the pubic symphysis, the sacroiliac joints, and other sites usually results from hematogenous distribution of injected organisms or septic venous thrombi. Pain and fever precede radiographic changes, sometimes by several weeks. While *S aureus*—often methicillin-resistant—is most common, *Serratia*,

Pseudomonas, *Candida* (often not *C albicans*), and other pathogens rarely encountered in spontaneous bone or joint disease are found in persons who inject drugs.

► Treatment

A common and difficult clinical problem is management of a person known to inject drugs who presents with fever. In general, after obtaining appropriate cultures (blood, urine, and sputum if the chest radiograph is abnormal), empiric therapy is begun. If the chest radiograph is suggestive of a community-acquired pneumonia (consolidation), therapy for outpatient pneumonia is begun with ceftriaxone, 1 g intravenously every 24 hours, plus either azithromycin (500 mg orally or intravenously every 24 hours) or doxycycline (100 mg orally or intravenously twice daily). If the chest radiograph is suggestive of septic emboli (nodular infiltrates), therapy for presumed endocarditis is initiated, usually with vancomycin 15 mg/kg/dose every 12 hours intravenously (due to the high prevalence of MRSA and the possibility of enterococcus). If the chest radiograph is normal and no focal site of infection can be found, endocarditis is presumed. While awaiting the results of blood cultures, empiric treatment with vancomycin is started. If blood cultures are positive for organisms that frequently cause endocarditis in drug users (see above), endocarditis is presumed to be present and treated accordingly. In the instance of confirmed methicillin-susceptible *S aureus* infection, vancomycin should be discontinued and treatment initiated with cefazolin or an antistaphylococcal penicillin. If blood cultures are positive for an organism that is an unusual cause of endocarditis, evaluation for an occult source of infection should go forward. In this setting, a transesophageal echocardiogram may be quite helpful since it is 90% sensitive in detecting vegetations and a negative study is strong evidence against endocarditis. If blood cultures are negative and the patient responds to antibiotics, therapy should be continued for 7–14 days (oral therapy can be given once an initial response has occurred). In every patient, careful examination for an occult source of infection (eg, genitourinary, dental, sinus, gallbladder) should be done. Clinicians also can have a significant role to play in integrating treatment of opioid use disorder when patients present with infectious disease complications. This includes screening for opioid use disorder, undergoing specific training for and prescribing opioid use disorder medications, treatment of withdrawal symptoms, and linkage to community-based treatment after hospital discharge.

► When to Refer

- Any patient with suspected or proven infective endocarditis.
- Patients with persistent bacteremia.

► When to Admit

- Persons who inject drugs with fever.
- Patients with abscesses or progressive skin and soft tissue infection that require debridement.

Larney S et al. All-cause and cause-specific mortality among people using extramedical opioids: a systematic review and meta-analysis. *JAMA Psychiatry*. 2020;77:493. [PMID: 31876906]

Pericás JM et al. Prospective cohort study of infective endocarditis in people who inject drugs. *J Am Coll Cardiol*. 2021;77:544. [PMID: 33538252]

Schranz AJ et al. Trends in drug use-associated infective endocarditis and heart valve surgery, 2007 to 2017: a study of statewide discharge data. *Ann Intern Med*. 2019;170:31. [PMID: 30508432]

Zhang AY et al. The changing epidemiology of candidemia in the United States: injection drug use as an increasingly common risk factor—active surveillance in selected sites, United States, 2014–17. *Clin Infect Dis*. 2020;71:1732. [PMID: 31676903]

enteric adenoviruses), vibrios (*Vibrio cholerae*, *Vibrio parahaemolyticus*), enterotoxin-producing *E coli*, *Giardia lamblia*, cryptosporidia, and agents that can cause food-borne gastroenteritis. In developed countries, viruses (particularly norovirus) are an important cause of hospitalizations due to acute gastroenteritis among adults.

The term **food poisoning** denotes diseases caused by toxins present in consumed foods. When the incubation period is short (1–6 hours after consumption), the *toxin is usually preformed*. Vomiting is usually a major complaint, and fever is usually absent. Examples include intoxication from *S aureus* or *Bacillus cereus*, and toxin can be detected in the food. When the incubation period is longer—between 8 hours and 16 hours—the organism is present in the food and *produces toxin after being ingested*. Vomiting is less prominent, abdominal cramping is frequent, and fever is often absent. The best example of this disease is that due to *Clostridium perfringens*. Toxin can be detected in food or stool specimens.

The inflammatory and noninflammatory diarrheas discussed above can also be transmitted by food and water and usually have incubation periods between 12 and 72 hours. *Cyclospora*, cryptosporidia, and *Isospora* are protozoans capable of causing disease in both immunocompetent and immunocompromised patients. Characteristics of disease include profuse watery diarrhea that is prolonged but usually self-limited (1–2 weeks) in the immunocompetent patient but can be chronic in the compromised host. Epidemiologic features may be helpful in determining etiology. Recent hospitalization or antibiotic use suggests *C difficile*; recent foreign travel suggests *Salmonella*, *Shigella*, *Campylobacter*, *E coli*, or *V cholerae*; undercooked hamburger suggests STEC; outbreak in long-term care facility, school, or cruise ship suggests norovirus (including newly identified strains, eg, GII.4 Sydney); and fried rice consumption is associated with *B cereus* toxin. Prominent features of some of these causes of diarrhea are listed in Table 30–3.

► Treatment

A. General Measures

In general, *most cases of acute gastroenteritis are self-limited and do not require therapy other than supportive measures*. Treatment usually consists of replacement of fluids and electrolytes and, very rarely, management of hypovolemic shock and respiratory compromise. In mild diarrhea, increasing ingestion of juices and clear soups is adequate. In more severe cases of dehydration (postural light-headedness, decreased urination), oral glucose-based rehydration solutions can be used (Ceralyte, Pedialyte).

B. Specific Measures

In immunocompetent adults, empiric antimicrobial therapy for bloody diarrhea while waiting for results is recommended only with the following circumstances: (1) documented fever, abdominal pain, bloody diarrhea, and bacillary dysentery (frequent scant bloody stools, fever, abdominal cramps, tenesmus) presumptively due to *Shigella*; and (2) returning travelers with a temperature of at least 38.5°C or signs of sepsis.

ACUTE INFECTIOUS DIARRHEA

ESSENTIALS OF DIAGNOSIS

- ▶ Acute diarrhea: lasts < 2 weeks.
- ▶ Chronic diarrhea: lasts > 2 weeks.
- ▶ Mild diarrhea: ≤ 3 stools per day.
- ▶ Moderate diarrhea: ≥ 4 stools per day with local symptoms (abdominal cramps, nausea, tenesmus).
- ▶ Severe diarrhea: ≥ 4 stools per day with systemic symptoms (fever, chills, dehydration).

► General Considerations

Acute diarrhea can be caused by a number of different factors, including emotional stress, food intolerance, inorganic agents (eg, sodium nitrite), organic substances (eg, mushrooms, shellfish), medications, and infectious agents (including viruses, bacteria, and protozoa) (Table 30–3). From a diagnostic and therapeutic standpoint, it is helpful to classify infectious diarrhea into syndromes that produce inflammatory or bloody diarrhea and those that are noninflammatory, nonbloody, or watery. In general, the term “**inflammatory diarrhea**” suggests colonic involvement by invasive bacteria or parasites or by toxin production. Patients complain of frequent bloody, small-volume stools, often associated with fever, abdominal cramps, tenesmus, and fecal urgency. Common causes of this syndrome include *Shigella*, *Salmonella*, *Campylobacter*, *Yersinia*, invasive strains of *Escherichia coli*, and other Shiga-toxin-producing strains of *E coli* (STEC), *Entamoeba histolytica*, and *C difficile*. Tests for fecal leukocytes or the neutrophil marker lactoferrin are frequently positive, and definitive etiologic diagnosis requires stool culture. **Noninflammatory diarrhea** is generally milder and is caused by viruses or toxins that affect the small intestine and interfere with salt and water balance, resulting in large-volume watery diarrhea, often with nausea, vomiting, and cramps. Common causes of this syndrome include viruses (eg, rotavirus, norovirus, astrovirus,

Table 30–3. Acute bacterial diarrheas and "food poisoning" (listed in alphabetical order).

Organism	Incubation Period	Vomiting	Diarrhea	Fever	Associated Foods	Diagnosis	Clinical Features and Treatment
<i>Bacillus cereus</i> (diarrheal toxin)	10–16 hours	±	+++	–	Toxin in meats, stews, and gravy.	Clinical. Food and stool can be tested for toxin.	Abdominal cramps, watery diarrhea, and nausea lasting 24–48 hours. Supportive care.
<i>Bacillus cereus</i> (preformed toxin)	1–8 hours	+++	±	–	Reheated fried rice causes vomiting or diarrhea.	Clinical. Food and stool can be tested for toxin.	Acute onset, severe nausea and vomiting lasting 24 hours. Supportive care.
<i>Campylobacter jejuni</i>	2–5 days	±	+++	+	Raw or undercooked poultry, unpasteurized milk, water.	Stool culture on special medium.	Fever, diarrhea that can be bloody, cramps. Usually self-limited in 2–10 days. Treat with azithromycin. Fluoroquinolones can be used if susceptibility is confirmed. May be associated with Guillain-Barré syndrome.
<i>Clostridium botulinum</i>	12–72 hours	±	–	–	Clostridia grow in anaerobic acidic environment, eg, canned foods, fermented fish, foods held warm for extended periods.	Stool, serum, and food can be tested for toxin. Stool and food can be cultured.	Diplopia, dysphagia, dysphonia, respiratory embarrassment. Treatment requires clear airway, ventilation, and intravenous polyvalent antitoxin (see text). Symptoms can last for days to months.
<i>Clostridioides difficile</i>	Usually occurs after 7–10 days of antibiotics. Can occur after a single dose or several weeks after completion of antibiotics.	–	+++	++	Associated with antibacterial drugs; clindamycin and beta-lactams most commonly implicated. Fluoroquinolones associated with hypervirulent strains.	Stool tested for toxin.	Abrupt onset of diarrhea that may be bloody; fever. Vancomycin 125 mg orally four times per day or fidaxomicin 200 mg twice daily for 10 days.
<i>Clostridium perfringens</i>	8–16 hours	±	+++	–	Clostridia grow in rewarmed meat and poultry dishes and produce an enterotoxin.	Stools can be tested for enterotoxin or cultured.	Abrupt onset of profuse diarrhea, abdominal cramps, nausea; vomiting occasionally. Recovery usual without treatment in 24–48 hours. Supportive care; antibiotics not needed.
Enterohemorrhagic <i>Escherichia coli</i> , including Shiga-toxin-producing <i>E coli</i> strains (STEC)	1–8 days	+	+++	–	Undercooked beef, especially hamburger; unpasteurized milk and juice; raw fruits and vegetables.	Shiga-toxin-producing <i>E coli</i> can be cultured on special medium. Other toxins can be detected in stool.	Usually abrupt onset of diarrhea, often bloody; abdominal pain. In adults, it is usually self-limited to 5–10 days. In children, it is associated with hemolytic-uremic syndrome (HUS). Antibiotic therapy may increase risk of HUS. Plasma exchange may help patients with STEC-associated HUS.
Enterotoxigenic <i>E coli</i> (ETEC)	1–3 days	±	+++	±	Water, food contaminated with feces.	Stool culture. Special tests required to identify toxin-producing strains.	Watery diarrhea and abdominal cramps, usually lasting 3–7 days. In travelers, fluoroquinolones shorten disease.

(continued)

Table 30–3. Acute bacterial diarrheas and "food poisoning" (listed in alphabetical order). (continued)

Organism	Incubation Period	Vomiting	Diarrhea	Fever	Associated Foods	Diagnosis	Clinical Features and Treatment
Noroviruses and other caliciviruses	12–48 hours	++	+++	+	Shellfish and fecally contaminated foods touched by infected food handlers.	Clinical diagnosis with negative stool cultures. PCR available on stool.	Nausea, vomiting (more common in children), diarrhea (more common in adults), fever, myalgias, abdominal cramps. Lasts 12–60 hours. Supportive care.
Rotavirus	1–3 days	++	+++	+	Fecally contaminated foods touched by infected food handlers.	Immunoassay on stool.	Acute onset, vomiting, watery diarrhea that lasts 4–8 days. Supportive care.
<i>Salmonella</i> species	1–3 days	–	++	+	Eggs, poultry, unpasteurized milk, cheese, juices, raw fruits and vegetables.	Routine stool culture.	Gradual or abrupt onset of diarrhea and low-grade fever. No antimicrobials unless high risk (see text) or systemic dissemination is suspected. If susceptibility is confirmed, treatment with ceftriaxone, ciprofloxacin, TMP-SMZ, or amoxicillin is recommended. Prolonged carriage can occur.
<i>Shigella</i> species (mild cases)	24–48 hours	±	+	+	Food or water contaminated with human feces. Person to person spread.	Routine stool culture.	Abrupt onset of diarrhea, often with blood and pus in stools, cramps, tenesmus, and lethargy. Stool cultures are positive. Azithromycin, ciprofloxacin, and ceftriaxone are drugs of choice. Avoid fluoroquinolones if the ciprofloxacin MIC is 0.12 mcg/mL or greater even if the laboratory report identifies the isolate as susceptible. Do not give opioids. Often mild and self-limited.
<i>Staphylococcus</i> (preformed toxin)	1–8 hours	+++	±	±	Staphylococci grow in meats, dairy, and bakery products and produce enterotoxin.	Clinical. Food and stool can be tested for toxin.	Abrupt onset, intense nausea and vomiting for up to 24 hours, recovery in 24–48 hours. Supportive care.
<i>Vibrio cholerae</i>	24–72 hours	+	+++	–	Contaminated water, fish, shellfish, street vendor food.	Stool culture on special medium.	Abrupt onset of liquid diarrhea in endemic area. Needs prompt intravenous or oral replacement of fluids and electrolytes. Doxycycline is drug of choice if antibiotics are indicated. Ciprofloxacin, azithromycin, or ceftriaxone are alternatives.
<i>Vibrio parahaemolyticus</i>	2–48 hours	+	+	±	Undercooked or raw seafood.	Stool culture on special medium.	Abrupt onset of watery diarrhea, abdominal cramps, nausea and vomiting. Recovery is usually complete in 2–5 days.
<i>Yersinia enterocolitica</i>	24–48 hours	±	+	+	Undercooked pork, contaminated water, unpasteurized milk, tofu.	Stool culture on special medium.	Severe abdominal pain (appendicitis-like symptoms), diarrhea, fever. Polyarthritis, erythema nodosum in children. If severe, give TMP-SMZ. Alternatives are cefotaxime and ciprofloxacin. Without treatment, self-limited in 1–3 weeks.

MIC, minimum inhibitory concentration; PCR, polymerase chain reaction; TMP-SMX, trimethoprim-sulfamethoxazole.

Either a fluoroquinolone or azithromycin should be used as empiric antimicrobial therapy for bloody diarrhea. Empiric antibacterial treatment should be considered in immunocompromised people with severe illness and bloody diarrhea. Loperamide may be given to immunocompetent adults with acute watery diarrhea but should be avoided with *Shigella* infection or in suspected or proven toxic megacolon. Therapeutic recommendations for specific agents can be found elsewhere in this book.

Bányai K et al. Viral gastroenteritis. Lancet. 2018;392:175. [PMID: 30025810]
 Guery B et al. *Clostridioides difficile*: diagnosis and treatments. BMJ. 2019;366:l4609. [PMID: 31431428]

INFECTIOUS DISEASES IN THE RETURNING TRAVELER



- Most infections are common and self-limited.
- Identify patients with transmissible diseases that require isolation.
- The incubation period may be helpful in diagnosis.
 - Less than 3 weeks following exposure may suggest dengue, leptospirosis, and yellow fever.
 - More than 3 weeks suggests typhoid fever, malaria, and tuberculosis.

► General Considerations

The differential diagnosis of fever in the returning traveler is broad, ranging from self-limited viral infections to life-threatening illness. The evaluation is best done by identifying whether a particular syndrome is present, then refining the differential diagnosis based on an exposure history. The travel history should include directed questions regarding geography (rural versus urban, specific country and region visited), time of year, animal or arthropod contact, unprotected sexual intercourse, ingestion of untreated water or raw foods, historical or pretravel immunizations, and adherence to malaria prophylaxis.

► Etiologies

The most common infectious causes of fever—excluding simple causes such as upper respiratory infections, bacterial pneumonia and urinary tract infections—in returning travelers are malaria (see Chapter 35), diarrhea (see next section), and dengue (see Chapter 32). Others include mononucleosis (associated with Epstein-Barr virus or cytomegalovirus), respiratory infections, including seasonal influenza, influenza A/H1N1 “swine” influenza, and influenza A/H5N1 or A/H7N9 “avian” influenza (see Chapter 32); leptospirosis (see Chapter 34); typhoid fever (see Chapter 33); and rickettsial infections (see Chapter 32). In recent years, coronaviruses have emerged as particularly

significant regional and global outbreaks of various sizes (SARS-CoV, MERS-CoV, and the massive global pandemic from SARS-CoV-2). Foreign travel is increasingly recognized as a risk factor for colonization and disease with resistant pathogens, such as ESBL-producing gram-negative organisms. Systemic febrile illnesses without a diagnosis also occur commonly, particularly in travelers returning from sub-Saharan Africa or Southeast Asia.

A. Fever and Rash

Potential etiologies include dengue, Ebola, Chikungunya, and Zika viruses, viral hemorrhagic fever, leptospirosis, meningococcemia, yellow fever, typhus, *Salmonella typhi*, and acute HIV infection.

B. Pulmonary Infiltrates

Tuberculosis, ascaris, *Paragonimus*, and *Strongyloides* can all cause pulmonary infiltrates.

C. Meningoencephalitis

Etiologies include *N meningitidis*, leptospirosis, arboviruses, rabies, and (cerebral) malaria.

D. Jaundice

Consider hepatitis A, yellow fever, hemorrhagic fever, leptospirosis, and malaria.

E. Fever Without Localizing Symptoms or Signs

Malaria, typhoid fever, acute HIV infection, rickettsial illness, visceral leishmaniasis, trypanosomiasis, and dengue are possible etiologies.

F. Traveler's Diarrhea

See next section.

► Clinical Findings

Fever and rash in the returning traveler should prompt blood cultures and serologic tests based on the exposure history. The workup of a pulmonary infiltrate should include the placement of a PPD or use of an interferon-gamma release assay, examination of sputum for acid-fast bacilli and possibly for ova and parasites. Patients with evidence of meningoencephalitis should receive lumbar puncture, blood cultures, thick/thin smears of peripheral blood, history-guided serologies, and a nape biopsy (if rabies is suspected). Jaundice in a returning traveler should be evaluated for hemolysis (for malaria), and the following tests should be performed: liver biochemical tests, thick/thin smears of peripheral blood, and directed serologic testing. The workup of traveler's diarrhea is presented in the following section. Finally, patients with fever but no localizing signs or symptoms should have blood cultures performed. Routine laboratory studies usually include complete blood count with differential, electrolytes, liver biochemical tests, urinalysis, and blood cultures. Thick and thin peripheral blood smears should be done (and repeated in 12–24 hours if clinical suspicion

remains high) for malaria if there has been travel to endemic areas. Other studies are directed by the results of history, physical examination, and initial laboratory tests. They may include stool for ova and parasites, chest radiograph, HIV test, and specific serologies (eg, dengue, leptospirosis, rickettsial disease, schistosomiasis, *Strongyloides*). Bone marrow biopsy to diagnose typhoid fever could be helpful in the appropriate patient. Increasingly, next-generation sequencing of plasma or body fluids such as cerebrospinal fluid is used as an adjunctive modality for diagnosis when traditional methods have not yielded a diagnosis.

► When to Refer

Travelers with fever, particularly if immunocompromised.

► When to Admit

Any evidence of hemorrhage, respiratory distress, hemodynamic instability, and neurologic deficits.

Buss I et al. Aetiology of fever in returning travellers and migrants: a systematic review and meta-analysis. *J Travel Med*. 2020;27:taaa207. [PMID: 33146395]

Gleeson SE et al. Recurrent hematochezia in a returning traveler. *JAMA*. 2021;325:1558. [PMID: 33666646]

Huang C et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497. [PMID: 31986264]

Polen KD et al. Update: interim guidance for preconception counseling and prevention of sexual transmission of Zika virus for men with possible Zika virus exposure—United States, August 2018. *MMWR Morb Mortal Wkly Rep*. 2018;67:868. [PMID: 30091965]

flora. Chronic watery diarrhea may be due to amebiasis or giardiasis or, rarely, tropical sprue.

► Clinical Findings

A. Symptoms and Signs

There may be up to ten or even more loose stools per day, often accompanied by abdominal cramps and nausea, occasionally by vomiting, and rarely by fever. The stools are usually watery and not associated with fever when caused by enterotoxigenic *E coli*. With invasive bacterial pathogens (*Shigella*, *Campylobacter*, *Salmonella*), stools can be bloody and fever may be present. The illness usually subsides spontaneously within 1–5 days, although 10% remain symptomatic for 1 week or longer, and symptoms persist for longer than 1 month in 2%. Traveler's diarrhea is also a significant risk factor for developing irritable bowel syndrome.

B. Laboratory Findings

In patients with fever and bloody diarrhea, stool culture is indicated, but in most cases, cultures are reserved for those who do not respond to antibiotics.

► Prevention

A. General Measures

Avoidance of fresh foods and water sources that are likely to be contaminated is recommended for travelers to developing countries, where infectious diarrheal illnesses are endemic.

B. Specific Measures

Because not all travelers will have diarrhea and because most episodes are brief and self-limited, the recommended approach is to *provide the traveler with a supply of antimicrobials*. Prophylaxis is recommended for those with significant underlying disease (inflammatory bowel disease, AIDS, diabetes mellitus, heart disease in older adults, conditions requiring immunosuppressive medications) and for those whose full activity status during the trip is so essential that even short periods of diarrhea would be unacceptable.

Prophylaxis is started upon entry into the destination country and is continued for 1 or 2 days after leaving. For stays of more than 3 weeks, prophylaxis is not recommended because of the cost and increased toxicity. For prophylaxis, several oral antimicrobial once-daily regimens are effective, such as ciprofloxacin, 500 mg, or rifaximin, 200 mg. Bismuth subsalicylate is effective but turns the tongue and the stools black and can interfere with doxycycline absorption, which may be needed for malaria prophylaxis; it is rarely used.

► Treatment

For most individuals, the affliction is short-lived, and symptomatic therapy with loperamide is all that is required, provided the patient is not systemically ill (fever 39°C or higher) and does not have dysentery (bloody stools), in which case antimotility agents should be avoided. Packages

TRAVELER'S DIARRHEA



ESSENTIALS OF DIAGNOSIS

- Usually a benign, self-limited disease occurring about 1 week into travel.
- Prophylaxis *not* recommended unless there is a comorbid disease (inflammatory bowel syndrome, HIV, immunosuppressive medication).
- Single-dose therapy of a fluoroquinolone usually effective if significant symptoms develop.

► General Considerations

Whenever a person travels from one country to another—particularly if the change involves a marked difference in climate, social conditions, or sanitation standards and facilities—diarrhea may develop within 2–10 days. Bacteria cause 80% of cases of traveler's diarrhea, with enterotoxigenic *E coli*, *Shigella* species, and *Campylobacter jejuni* being the most common pathogens. Less common are *Aeromonas*, *Salmonella*, noncholera vibrios, *E histolytica*, and *G lamblia*. Contributory causes include unusual food and drink, change in living habits, occasional viral infections (adenoviruses or rotaviruses), and change in bowel

of oral rehydration salts to treat dehydration are available over the counter in the United States (Infalyte, Pedialyte, others) and in many foreign countries.

When treatment is necessary, in areas where toxin-producing bacteria are the major cause of diarrhea (Latin America and Africa), loperamide (4 mg oral loading dose, then 2 mg after each loose stool to a maximum of 16 mg/day) with a single oral dose of ciprofloxacin (750 mg), levofloxacin (500 mg), or ofloxacin (200 mg) cures most cases of traveler's diarrhea. If diarrhea is associated with bloody stools or persists despite a single dose of a fluoroquinolone, 1000 mg of azithromycin should be taken. In pregnant women and in areas where invasive bacteria more commonly cause diarrhea (Indian subcontinent, Asia, especially Thailand where fluoroquinolone-resistant *Campylobacter* is prevalent), azithromycin is the medication of choice. Rifaximin, a nonabsorbable agent, is also approved for therapy of traveler's diarrhea at a dose of 200 mg orally three times per day or 400 mg twice a day for 3 days. Because luminal concentrations are high, but tissue levels are insufficient, it should not be used in situations where there is a high likelihood of invasive disease (eg, fever, systemic toxicity, or bloody stools).

► When to Refer

- Cases refractory to treatment.
- Persistent infection.
- Immunocompromised patient.

► When to Admit

Patients who are severely dehydrated or hemodynamically unstable should be admitted to the hospital.

Ashbaugh HR et al. A multisite network assessment of the epidemiology and etiology of acquired diarrhea among U.S. military and western travelers (Global Travelers' Diarrhea Study): a principal role of norovirus among travelers with gastrointestinal illness. *Am J Trop Med Hyg*. 2020;103:1855. [PMID: 32959765]

Schweitzer L et al. Emerging concepts in the diagnosis, treatment, and prevention of travelers' diarrhea. *Curr Opin Infect Dis*. 2019;32:468. [PMID: 31361658]

ANTIMICROBIAL THERAPY

SELECTED PRINCIPLES OF ANTIMICROBIAL THERAPY

Specific steps (outlined below) are required when considering antibiotic therapy for patients. Medications within classes, medications of first choice, and alternative medications are presented in Table 30–4.

A. Etiologic Diagnosis

Based on the organ system involved, the organism causing infection can often be predicted. See Tables 30–5 and 30–6.

B. "Best Guess"

Select an empiric regimen that is likely to be effective against the suspected pathogens.

C. Laboratory Control

Specimens for laboratory examination should be obtained before institution of therapy to determine susceptibility.

D. Clinical Response

Based on clinical response and other data, the laboratory reports are evaluated and then the desirability of changing the regimen is considered. If the specimen was obtained from a normally sterile site (eg, blood, cerebrospinal fluid, pleural fluid, joint fluid), the recovery of a microorganism in significant amounts is meaningful even if the organism recovered is different from the clinically suspected agent, and this may force a change in treatment. Isolation of unexpected microorganisms from the respiratory tract, gastrointestinal tract, or surface lesions (sites that have a complex flora) may represent colonization or contamination, and cultures must be critically evaluated before medications are abandoned that were judiciously selected on a "best guess" basis.

E. Drug Susceptibility Tests

Some microorganisms are predictably inhibited by certain medications; if such organisms are isolated, they need not be tested for drug susceptibility. For example, all group A hemolytic streptococci are inhibited by penicillin. Other organisms (eg, enteric gram-negative rods) are variably susceptible and generally require susceptibility testing whenever they are isolated. Organisms that once had predictable susceptibility patterns are now associated with resistance and require testing. Examples include the pneumococci, which may be resistant to multiple medications (including penicillin, macrolides, and tetracyclines); the enterococci, which may be resistant to penicillin, aminoglycosides, and vancomycin; and ESBL producing-*E coli* resistant to third-generation cephalosporins, aminoglycosides, and fluoroquinolones.

When culture and susceptibility results have been finalized, clinicians must use the most narrow-spectrum agent and the shortest duration possible to decrease the selection pressure for antibacterial resistance.

Antimicrobial drug susceptibility tests may be performed on solid media as disk diffusion tests, in broth, in tubes, in wells of microdilution plates, or as E-tests (strips with increasing concentration of antibiotic). The latter three methods yield results expressed as MIC. In most infections, the MIC is the appropriate in vitro test to guide selection of an antibacterial agent. When there appear to be marked discrepancies between susceptibility testing and clinical response, the following possibilities must be considered:

1. Selection of an inappropriate medication, medication dosage, or route of administration.
2. Failure to drain a collection of pus or to remove a foreign body.

Table 30–4. Medication of choice for suspected or documented microbial pathogens (listed in alphabetical order, within classes).

Suspected or Proved Etiologic Agent	Medication(s) of First Choice	Alternative Medication(s)
Gram-Negative Cocci		
<i>Moraxella catarrhalis</i>	Cefuroxime, amoxicillin-clavulanic acid	Ceftriaxone, cefuroxime axetil, a fluoroquinolone, ¹ a macrolide, ² a tetracycline, ³ TMP-SMZ ⁴
<i>Neisseria gonorrhoeae</i> (gonococcus)	Ceftriaxone + azithromycin or doxycycline	Cefixime + azithromycin or doxycycline ⁵
<i>Neisseria meningitidis</i> (meningococcus)	Penicillin ⁶	Ceftriaxone, ampicillin
Gram-Positive Cocci		
<i>Enterococcus faecalis</i>	Ampicillin ± gentamicin ⁷ Ampicillin ± ceftriaxone	Vancomycin ± gentamicin
<i>Enterococcus faecium</i>	Vancomycin ± gentamicin ⁷	Linezolid, ⁸ quinupristin-dalfopristin, ⁸ daptomycin, ⁸ tigecycline, ⁸ tedizolid, ⁸ oritavancin ⁸
<i>Staphylococcus</i> , methicillin-susceptible	Cefazolin or Penicillinase-resistant penicillin ¹⁰	Vancomycin, a cephalosporin, ⁹ clindamycin, amoxicillin-clavulanic acid, ampicillin-sulbactam
<i>Staphylococcus</i> , methicillin-resistant	Vancomycin	TMP-SMZ, ⁴ doxycycline, minocycline, linezolid, ⁸ tedizolid, ⁸ daptomycin, ⁸ televancin, ⁸ dalbavancin, ⁸ oritavancin, ⁸ ceftaroline, delafloxacin
<i>Streptococcus</i> , hemolytic, groups A, B, C, G	Penicillin ⁶	Macrolide, ² a cephalosporin, ⁹ vancomycin, clindamycin
<i>Streptococcus pneumoniae</i> ¹¹ (pneumococcus)	Penicillin ⁶	A cephalosporin, ⁹ vancomycin, clindamycin, a tetracycline, ³ respiratory fluoroquinolones ¹
Viridans streptococci	Penicillin ⁶	Cephalosporin, ⁹ vancomycin
Gram-Negative Rods		
<i>Acinetobacter</i>	Imipenem, meropenem	Tigecycline, minocycline, doxycycline, aminoglycosides, ¹² colistin, ceferocol
<i>Bacteroides</i> , gastrointestinal strains	Metronidazole	Ampicillin-sulbactam, piperacillin-tazobactam, ertapenem
<i>Brucella</i>	Doxycycline + rifampin ³	TMP-SMZ ⁴ ± gentamicin; ciprofloxacin + rifampin
<i>Burkholderia mallei</i> (glanders)	Streptomycin + tetracycline ³	Chloramphenicol + streptomycin
<i>Burkholderia pseudomallei</i> (melioidosis)	Ceftazidime	Tetracycline, ³ TMP-SMZ, ⁴ amoxicillin-clavulanic acid, imipenem or meropenem
<i>Campylobacter jejuni</i>	Azithromycin	A fluoroquinolone ¹
<i>Enterobacter</i>	Ertapenem, imipenem, meropenem, cefepime	Aminoglycoside, a fluoroquinolone, ¹ TMP-SMZ ⁴
<i>Escherichia coli</i> (uncomplicated outpatient urinary infection)	Nitrofurantoin, fosfomycin	Fluoroquinolones, ¹ TMP-SMZ, ⁴ oral cephalosporin
<i>Escherichia coli</i> (sepsis) ¹³	Cefotaxime, ceftriaxone	Ertapenem, ¹³ imipenem ¹³ or meropenem, ¹³ aminoglycosides, ¹² aztreonam, ticarcillin-clavulanate, piperacillin-tazobactam, ceftazidime-avibactam, ^{13,15} ceftolozane-tazobactam, ^{13,14} meropenem/vaborbactam, ¹⁵ imipenem/cilastatin-relebactam ^{13,14,15}
<i>Haemophilus</i> (respiratory infections, otitis)	Ampicillin-clavulanate	Doxycycline, azithromycin, ceftriaxone, cefuroxime, cefuroxime axetil, TMP-SMZ ⁴
<i>Haemophilus</i> (serious infection)	Ceftriaxone	Aztreonam
<i>Helicobacter pylori</i>	Proton pump inhibitor (PPI), clarithromycin, amoxicillin, and metronidazole	PPI, clarithromycin, and amoxicillin or metronidazole

(continued)

Table 30–4. Medication of choice for suspected or documented microbial pathogens (listed in alphabetical order, within classes). (continued)

Suspected or Proved Etiologic Agent	Medication(s) of First Choice	Alternative Medication(s)
Gram-Negative Rods (Cont.)		
<i>Klebsiella</i> ¹³	Ceftriaxone	TMP-SMZ, ⁴ aminoglycoside, ¹² ertapenem, ¹³ imipenem ¹³ or meropenem, ¹³ a fluoroquinolone, ¹ aztreonam, ticarcillin-clavulanate, piperacillin-tazobactam, ceftazidime-avibactam, ¹³ ceftolozane-tazobactam, ^{13,14} meropenem/vaborbactam, ¹⁵ imipenem/cilastatin-relebactam ^{13,14,15}
<i>Legionella</i> species (pneumonia)	Azithromycin, or fluoroquinolones ¹ ± rifampin	Doxycycline ± rifampin
<i>Prevotella</i> , oropharyngeal strains	Clindamycin	Metronidazole
<i>Proteus mirabilis</i>	Ampicillin	TMP-SMZ, ⁴ a fluoroquinolone, ¹ a cephalosporin ⁹
<i>Proteus vulgaris</i> and other species (<i>Morganella</i> , <i>Providencia</i>)	Ceftriaxone	Ertapenem, imipenem or meropenem, TMP-SMZ, ⁴ a fluoroquinolone ¹
<i>Pseudomonas aeruginosa</i>	Piperacillin-tazobactam or ceftazidime or cefepime, or imipenem or meropenem or doripenem or aztreonam (any one of the previous agents) ± aminoglycoside ¹²	Ciprofloxacin (or levofloxacin) ± piperacillin-tazobactam; ciprofloxacin (or levofloxacin) ± ceftazidime; ciprofloxacin (or levofloxacin) ± cefepime; ceftazidime-avibactam ¹³ ; ceftolozane-tazobactam, ¹³ cefiderocol, imipenem/cilastatin-relebactam, meropenem/vaborbactam
<i>Salmonella</i> (bacteremia)	Ceftriaxone	A fluoroquinolone ¹
<i>Serratia</i>	Carbapenem	TMP-SMZ, ⁴ a fluoroquinolone, ¹ ceftriaxone
<i>Shigella</i>	Azithromycin, ciprofloxacin, or ceftriaxone	TMP-SMZ ⁴
<i>Vibrio</i> (cholera, sepsis)	A tetracycline ³	TMP-SMZ, ⁴ a fluoroquinolone ¹
<i>Yersinia pestis</i> (plague)	Streptomycin ± a tetracycline ³	Chloramphenicol, TMP-SMZ ⁵
Gram-Positive Rods		
<i>Actinomyces</i>	Penicillin ⁶	Tetracycline, ³ clindamycin
<i>Bacillus</i> (including anthrax)	Penicillin ⁶	A macrolide, ² a fluoroquinolone ¹
<i>Clostridium</i> (eg, gas gangrene, tetanus)	Penicillin ⁶	Metronidazole, clindamycin, imipenem, or meropenem
<i>Corynebacterium diphtheriae</i>	Macrolide ²	Penicillin ⁶
<i>Corynebacterium jeikeium</i>	Vancomycin	Linezolid
<i>Listeria</i>	Ampicillin ± aminoglycoside ¹²	TMP-SMZ ⁴
Acid-Fast Rods		
<i>Mycobacterium avium</i> complex	Clarithromycin or azithromycin + ethambutol, ± rifabutin	Amikacin, ciprofloxacin
<i>Mycobacterium fortuitum-chelonei</i>	Cefoxitin + clarithromycin	Amikacin, rifampin, sulfonamide, doxycycline, linezolid
<i>Mycobacterium kansasii</i>	INH + rifampin ± ethambutol	Clarithromycin, azithromycin, ethionamide, cycloserine
<i>Mycobacterium leprae</i>	Dapsone + rifampin ± clofazimine	Minocycline, ofloxacin, clarithromycin
<i>Mycobacterium tuberculosis</i> ¹⁶	Isoniazid (INH) + rifampin + pyrazinamide ± ethambutol	Other antituberculous drugs (see Tables 9–14 and 9–15)
<i>Nocardia</i>	TMP-SMZ ⁴	Minocycline, imipenem or meropenem, linezolid
Spirochetes		
<i>Borrelia burgdorferi</i> (Lyme disease)	Doxycycline, amoxicillin, cefuroxime axetil	Ceftriaxone, penicillin, azithromycin
<i>Borrelia recurrentis</i> (relapsing fever)	Doxycycline ³	Penicillin ⁶

(continued)

Table 30–4. Medication of choice for suspected or documented microbial pathogens (listed in alphabetical order, within classes). (continued)

Suspected or Proved Etiologic Agent	Medication(s) of First Choice	Alternative Medication(s)
Spirochetes (Cont.)		
<i>Leptospira</i>	Penicillin ⁶	Doxycycline, ³ ceftriaxone
<i>Treponema pallidum</i> (syphilis)	Penicillin ⁶	Doxycycline, ceftriaxone
<i>Treponema pertenue</i> (yaws)	Penicillin ⁶	Doxycycline
Mycoplasmas	Azithromycin or doxycycline	A fluoroquinolone¹
Chlamydiae		
<i>C pneumoniae</i>	Doxycycline ³	Azithromycin, a fluoroquinolone ^{1,17}
<i>C psittaci</i>	Doxycycline	Chloramphenicol
<i>C trachomatis</i> (urethritis or pelvic inflammatory disease)	Doxycycline or azithromycin	Levofloxacin, ofloxacin
Rickettsiae	Doxycycline³	Chloramphenicol, a fluoroquinolone¹

¹Fluoroquinolones include ciprofloxacin, levofloxacin, moxifloxacin, and others. Gemifloxacin, levofloxacin, and moxifloxacin, the so-called respiratory fluoroquinolones, demonstrate the most reliable activity against penicillin-resistant *S pneumoniae* and other respiratory infection pathogens. Delafloxacin is predictably active against methicillin-resistant *S aureus* (MRSA).

²Azithromycin is the preferred macrolide due to increased safety profile and minimal drug interaction potential.

³All tetracyclines have similar activity against most microorganisms. Minocycline (the most active tetracycline) and doxycycline are more active than tetracycline against *S aureus*.

⁴TMP-SMZ is a mixture of 1 part trimethoprim and 5 parts sulfamethoxazole.

⁵Test of cure required if ceftriaxone not used.

⁶Penicillin G is preferred for parenteral injection; penicillin V for oral administration.

⁷Addition of gentamicin indicated only for severe enterococcal infections (eg, endocarditis, meningitis).

⁸Linezolid, tedizolid, daptomycin, televancin, dalbavancin, and oritavancin should be reserved for the treatment of vancomycin-resistant isolates or in patients intolerant of vancomycin.

⁹Most intravenous cephalosporins (with the exception of ceftazidime) are active against streptococci and methicillin-susceptible staphylococci.

¹⁰Parenteral nafcillin or oxacillin; oral dicloxacillin, cloxacillin, or oxacillin.

¹¹Infections caused by isolates with intermediate resistance may respond to high dose penicillin or ceftriaxone or the respiratory fluoroquinolones (gemifloxacin, levofloxacin, and moxifloxacin). Infections caused by highly penicillin-resistant isolates should be treated with vancomycin. Penicillin-resistant pneumococci are often resistant to macrolides, tetracyclines, and TMP-SMZ.

¹²Aminoglycosides—gentamicin, tobramycin, amikacin, netilmicin, plazomicin—should be chosen on the basis of local patterns of susceptibility.

¹³Extended beta-lactamase-producing (ESBL) isolates should be treated with a carbapenem. If a carbapenem cannot be used, ceftazidime-avibactam or possibly ceftolozane-tazobactam can be considered.

¹⁴Ceftolozane-tazobactam, cefiderocol, imipenem/cilastatin-relebactam and occasionally ceftazidime-avibactam may be active against multidrug-resistant *P aeruginosa*.

¹⁵Consider in cases of infection due to carbapenemase-producing Enterobacteriaceae.

¹⁶Resistance is common and susceptibility testing must be performed.

¹⁷Ciprofloxacin has inferior antichlamydial activity compared with levofloxacin or ofloxacin.

±, alone or combined with.

- Failure of a poorly diffusing drug to reach the site of infection (eg, CNS) or to reach intracellular phagocytosed bacteria.
- Superinfection in the course of prolonged chemotherapy.
- Emergence of drug resistance in the original pathogen or superinfection with a new more resistant organism.
- Participation of two or more microorganisms in the infectious process, of which only one was originally detected and used for medication selection.
- Inadequate host defenses, including immunodeficiencies and diabetes mellitus.
- Noninfectious causes, including drug fever, malignancy, and autoimmune disease.

F. Promptness of Response

Response depends on a number of factors, including the patient (immunocompromised patients respond slower than immunocompetent patients), the site of infection (deep-seated infections such as osteomyelitis and endocarditis respond more slowly than superficial infections such as cystitis or cellulitis), the pathogen (virulent organisms such as *S aureus* respond more slowly than viridans streptococci; mycobacterial and fungal infections respond slower than bacterial infections), and the duration of illness (in general, the longer the symptoms are present, the longer it takes to respond). Thus, depending on the clinical situation, persistent fever and leukocytosis several days

Table 30–5. Examples of initial antimicrobial therapy for acutely ill, hospitalized adults pending identification of causative organism (in alphabetical order).

Suspected Clinical Diagnosis	Likely Etiologic Diagnosis	Medication of Choice
Brain abscess	Mixed anaerobes, pneumococci, streptococci	Ceftriaxone, 2 g intravenously every 12 hours plus metronidazole, 500 mg orally every 8 hours, plus vancomycin, 15 mg/kg intravenously every 8 hours ¹
Endocarditis, acute (including injection drug user)	<i>S aureus</i> , <i>E faecalis</i> , viridans streptococci	Vancomycin, 15 mg/kg/dose intravenously every 12 hours ¹
Fever in neutropenic patient receiving cancer chemotherapy	<i>S aureus</i> , <i>Pseudomonas</i> , <i>Klebsiella</i> , <i>E coli</i>	Cefepime, 2 g intravenously every 8 hours
Intra-abdominal sepsis (eg, post-operative, peritonitis, cholecystitis)	Gram-negative bacteria, <i>Bacteroides</i> , anaerobic bacteria, enterococcus	Piperacillin-tazobactam, 4.5 g intravenously every 6–8 hours, or ertapenem, 1 g every 24 hours
Meningitis, bacterial, age > 50, community-acquired	Pneumococcus, meningococcus, <i>Listeria monocytogenes</i> , ² gram-negative bacilli, group B streptococcus	Ampicillin, 2 g intravenously every 4 hours, plus ceftriaxone, 2 g intravenously every 12 hours, plus vancomycin, 15 mg/kg intravenously every 8 hours ¹
Meningitis, bacterial, community-acquired	<i>Streptococcus pneumoniae</i> (pneumococcus), ² <i>Neisseria meningitidis</i> (meningococcus)	Ceftriaxone, 2 g intravenously every 12 hours, ³ plus vancomycin, 15 mg/kg intravenously every 8 hours ¹
Meningitis, postoperative (or posttraumatic)	<i>S aureus</i> , gram-negative bacilli, coagulase-negative staphylococci, diphtheroids (eg, <i>Propionibacterium acnes</i>) (uncommon) pneumococcus (in posttraumatic)	Vancomycin, 15 mg/kg intravenously every 8 hours ¹ , plus cefepime, 3 g intravenously every 8 hours ⁴
Osteomyelitis	<i>S aureus</i> , secondarily gram-negative aerobes	Vancomycin 15 mg/kg intravenously every 8 hours ¹ , plus ceftriaxone 2 g intravenously every 24 hours
Pneumonia, acute, community-acquired, non-ICU hospital admission	Pneumococci, <i>M pneumoniae</i> , <i>Legionella</i> , <i>C pneumoniae</i>	Ceftriaxone, 1 g intravenously every 24 hours or ampicillin-sulbactam 1.5–3 g intravenously every 6 hours) plus azithromycin, 500 mg intravenously every 24 hours; or a respiratory fluoroquinolone ⁵ alone
Pneumonia, postoperative or nosocomial	<i>S aureus</i> , mixed anaerobes, gram-negative bacilli	Cefepime, 2 g intravenously every 8 hours; or ceftazidime, 2 g intravenously every 8 hours; or piperacillin-tazobactam, 4.5 g intravenously every 6–8 hours; or imipenem, 500 mg intravenously every 6 hours; or meropenem, 1 g intravenously every 8 hours plus tobramycin, 5–7 mg/kg intravenously every 24 hours; or ciprofloxacin, 400 mg intravenously every 12 hours; or levofloxacin, 500 mg intravenously every 24 hours plus vancomycin, 15 mg/kg/dose intravenously every 12 hours ¹
Pyelonephritis with flank pain and fever (recurrent urinary tract infection)	<i>E coli</i> , <i>Klebsiella</i> , <i>Enterobacter</i> , <i>Pseudomonas</i>	Ceftriaxone, 1 g intravenously every 24 hours; or if culture results confirm susceptibility, ciprofloxacin, 400 mg intravenously every 12 hours (500 mg orally); or levofloxacin, 500 mg once daily (intravenously/orally)
Septic arthritis	<i>S aureus</i> , <i>N gonorrhoeae</i>	Ceftriaxone, 1–2 g intravenously every 24 hours
Septic thrombophlebitis (eg, IV tubing, IV shunts)	<i>S aureus</i> , gram-negative aerobic bacteria	Vancomycin, 15 mg/kg/dose intravenously every 12 hours ¹ , plus ceftriaxone, 1 g intravenously every 24 hours

¹Vancomycin serum levels should be monitored.²TMP-SMZ can be used to treat *Listeria monocytogenes* in patients allergic to penicillin in a dosage of 15–20 mg/kg/day of TMP in three or four divided doses.³Including penicillin nonsusceptible isolates.⁴Cefepime 3 g is a higher dose than sometimes recommended in order to optimize treatment of *Pseudomonas* and *Enterobacter*.⁵Levofloxacin 750 mg/day, moxifloxacin 400 mg/day.

Table 30–6. Examples of empiric choices of antimicrobials for adult outpatient infections (in alphabetical order).

Suspected Clinical Diagnosis	Likely Etiologic Agents	Medications of Choice	Alternative Medications
Acute sinusitis	<i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Moraxella catarrhalis</i>	Amoxicillin-clavulanate, ¹ 875 mg orally twice daily for 10 days	For patients allergic to penicillin, doxycycline, 100 mg twice daily for 10 days
Aspiration pneumonia	Mixed oropharyngeal flora, including anaerobes	Clindamycin, 300 mg orally four times daily for 10–14 days	Amoxicillin 500 mg orally three times daily for 10–14 days
Cystitis	<i>Escherichia coli</i> , <i>Staphylococcus saprophyticus</i> , <i>Klebsiella pneumoniae</i> , <i>Proteus</i> species, other gram-negative rods or enterococci	Nitrofurantoin monohydrate macro-crystals 100 mg twice daily for 5–7 days (unless pregnant); fosfomycin 3 g orally as a single dose	Cephalexin, 500 mg orally four times daily for 7 days, for uncomplicated cystitis. Due to increasing bacterial resistance, TMP-SMZ and fluoroquinolones are not recommended as first-line therapy for empiric treatment
Erysipelas, impetigo, cellulitis, ascending lymphangitis	Group A streptococcus	Penicillin V, 500 mg orally four times daily for 7–10 days	Cephalexin, 500 mg orally four times daily for 7–10 days; or azithromycin, 500 mg on day 1 and 250 mg on days 2–5
Furuncle with surrounding cellulitis	<i>Staphylococcus aureus</i>	Dicloxacillin, 500 mg orally four times daily for 7–10 days for MSSA. For CA-MRSA: TMP-SMZ ² one double-strength tablet twice daily for 7–10 days; or clindamycin 300 mg orally three times daily for 7–10 days	Cephalexin, 500 mg orally four times daily for 7–10 days for MSSA. For CA-MRSA, doxycycline is a reasonable alternative
Gastroenteritis	<i>Salmonella</i> , <i>Shigella</i> , <i>Campylobacter</i> , <i>Entamoeba histolytica</i>	See footnote 3	
Otitis media	<i>S pneumoniae</i> , <i>H influenzae</i> , <i>M catarrhalis</i>	Amoxicillin, 500 mg–1 g orally three times daily for 10 days	Amoxicillin-clavulanate, ¹ 875 mg orally twice daily; or cefuroxime, 500 mg orally twice daily; or cefpodoxime, 200–400 mg daily; or doxycycline, 100 mg twice daily
Pelvic inflammatory disease	<i>Neisseria gonorrhoeae</i> , <i>Chlamydia trachomatis</i> , anaerobes, gram-negative rods	Ceftriaxone 250 mg intramuscularly once plus doxycycline 100 mg orally twice daily for 14 days +/- metronidazole 500 mg orally twice daily for 14 days; or cefoxitin 2 g intramuscularly once plus probenecid 1 g orally once, plus doxycycline 100 mg orally twice daily for 14 days +/- metronidazole 500 mg orally twice daily for 14 days	
Pharyngitis	Group A streptococcus	Penicillin V, 500 mg orally four times daily, or amoxicillin, 500 mg–1 g orally three times daily for 10 days	For patients with history of mild penicillin allergy, cephalexin, 500 mg orally four times daily for 10 days; for patients with IgE-mediated reaction, clindamycin, 300 mg orally four times daily for 10 days; or azithromycin, 500 mg on day 1 and 250 mg on days 2–5
Pneumonia	<i>S pneumoniae</i> , <i>Mycoplasma pneumoniae</i> , <i>Legionella pneumophila</i> , <i>Chlamydophila pneumoniae</i>	Amoxicillin, 1.0 g three times daily or Doxycycline, 100 mg orally twice daily	For patients at high risk for infection due to resistant pneumococci: amoxicillin-clavulanate or cefpodoxime or cefuroxime + macrolide or doxycycline or a respiratory fluoroquinolone ⁴
Pyelonephritis	<i>E coli</i> , <i>K pneumoniae</i> , <i>Proteus</i> species, <i>S saprophyticus</i>	Fluoroquinolones ⁵ for 7 days if prevalence of resistance among uropathogens is < 10%	TMP-SMZ, ² one double-strength tablet twice daily for 7–14 days for susceptible pathogens. Oral beta-lactams are less effective than fluoroquinolones or TMP-SMZ

(continued)

Table 30–6. Examples of empiric choices of antimicrobials for adult outpatient infections (in alphabetical order). (continued)

Suspected Clinical Diagnosis	Likely Etiologic Agents	Medications of Choice	Alternative Medications
Urethritis, epididymitis	<i>N gonorrhoeae</i> , <i>C trachomatis</i>	Ceftriaxone, 250 mg intramuscularly once plus azithromycin (or doxycycline) for <i>N gonorrhoeae</i> ; azithromycin 1 g orally once, or doxycycline, 100 mg orally twice daily for 7 days, for <i>C trachomatis</i>	Cefixime 400 mg orally once for <i>N gonorrhoeae</i> ⁶
Syphilis			
Early syphilis (primary, secondary, or latent of < 1 year's duration)	<i>T pallidum</i>	Benzathine penicillin G, 2.4 million units intramuscularly once	Doxycycline, 100 mg orally twice daily for 2 weeks. Ceftriaxone, 1–2 g intravenously once daily for 10–14 days
Latent syphilis of > 1 year's duration or cardiovascular syphilis	<i>T pallidum</i>	Benzathine penicillin G, 2.4 million units intramuscularly once a week for 3 weeks (total: 7.2 million units)	Doxycycline, 100 mg orally twice daily for 4 weeks
Neurosyphilis	<i>T pallidum</i>	Aqueous penicillin G, 18–24 million units/day intravenously for 10–14 days	

¹Amoxicillin-clavulanate is available as a combination of amoxicillin, 250 mg, 500 mg, or 875 mg, plus 125 mg of clavulanic acid. Augmentin XR is a combination of amoxicillin 1 g and clavulanic acid 62.5 mg.

²TMP-SMZ is a fixed combination of 1 part trimethoprim and 5 parts sulfamethoxazole. Single-strength tablets: 80 mg TMP, 400 mg SMZ; double-strength tablets: 160 mg TMP, 800 mg SMZ.

³The diagnosis should be confirmed by culture before therapy. *Salmonella* gastroenteritis does not require therapy. For susceptible *Shigella* isolates, give ciprofloxacin, 500 mg orally twice daily for 5 days. For *Campylobacter* infection, give azithromycin, 1 g orally times one dose, or ciprofloxacin, 500 mg orally twice daily for 5 days. For *E histolytica* infection, give metronidazole, 750 mg orally three times daily for 5–10 days, followed by diiodohydroxyquinoline (not available in United States), 650 mg orally three times daily for 3 weeks.

⁴Fluoroquinolones with activity against *S pneumoniae*, including penicillin-resistant isolates, include levofloxacin (500–750 mg orally once daily), moxifloxacin (400 mg orally once daily), or gemifloxacin (320 mg orally once daily). Use fluoroquinolones as medication of choice if recent non-fluoroquinolone antibiotic use within 3 months.

⁵Fluoroquinolones and dosages include ciprofloxacin, 500 mg orally twice daily; ofloxacin, 400 mg orally twice daily; levofloxacin, 500 mg orally daily.

⁶Test of cure recommended if ceftriaxone is not used.

CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus*; MRSA, methicillin-resistant *S aureus*; MSSA, methicillin-susceptible *S aureus*; TMP-SMZ, trimethoprim-sulfamethoxazole.

after initiation of therapy may not indicate improper choice of antibiotics but may be due to the natural history of the disease being treated. In most infections, either a bacteriostatic or a bactericidal agent can be used. In some infections (eg, infective endocarditis and meningitis), a bactericidal agent should be used. When potentially toxic medications (eg, aminoglycosides, flucytosine) are used, serum levels of the medication are measured to minimize toxicity and ensure appropriate dosage. In patients with altered renal or hepatic clearance of medications, the dosage or frequency of administration must be adjusted; it is best to measure levels in older adults, in morbidly obese patients, or in those with altered kidney function when possible and adjust therapy accordingly.

G. Duration of Antimicrobial Therapy

Generally, effective antimicrobial treatment results in reversal of the clinical and laboratory parameters of active

infection and marked clinical improvement. However, varying periods of treatment may be required for cure. Key factors include (1) the type of infecting organism (bacterial infections generally can be cured more rapidly than fungal or mycobacterial ones), (2) the location of the process (eg, endocarditis and osteomyelitis require prolonged therapy), and (3) the immunocompetence of the patient.

H. Adverse Reactions and Toxicity

These include hypersensitivity reactions, direct toxicity, superinfection by drug-resistant microorganisms, and drug interactions. If the infection is life-threatening and treatment cannot be stopped, the reactions are managed symptomatically or another medication is chosen that does not cross-react with the offending one (Table 30–4). If the infection is less serious, it may be possible to stop all antimicrobials and monitor the patient closely.

I. Route of Administration

Intravenous therapy is preferred for acutely ill patients with serious infections (eg, endocarditis, meningitis, sepsis, severe pneumonia) when dependable levels of antibiotics are required for successful therapy. Certain medications (eg, doxycycline, fluconazole, voriconazole, rifampin, metronidazole, TMP-SMZ, and fluoroquinolones) are so well absorbed that they generally can be administered orally in seriously ill—but not hemodynamically unstable—patients.

Food does not significantly influence the bioavailability of most oral antimicrobial agents. However, the tetracyclines (particularly tetracycline) and the quinolones chelate multivalent cations resulting in decreased oral bioavailability. Posaconazole suspension should always be administered with food.

A major complication of intravenous antibiotic therapy is infection due to the manipulation of the intravenous catheter. Peripheral catheters are changed every 48–72 hours to decrease the likelihood of catheter-associated infection, and antimicrobial-coated central venous catheters (minocycline and rifampin, chlorhexidine and sulfadiazine) have been associated with a decreased incidence of these infections. Most of these infections present with local signs of infection (erythema, tenderness) at the insertion site. In a patient with fever who is receiving intravenous therapy, the catheter must always be considered a potential source. Small-gauge (20–23F) peripherally inserted silicone or polyurethane catheters (Per Q Cath, A-Cath, Ven-A-Cath, and others) are associated with a low infection rate and can be maintained for 3–6 months without replacement. Such catheters are ideal for long-term outpatient antibiotic therapy.

J. Cost of Antibiotics

The cost of these agents can be substantial. In addition to acquisition costs and monitoring costs (drug levels, liver biochemical tests, electrolytes, etc), the cost of treating adverse reactions, the cost of treatment failure and superinfection, and the costs associated with drug administration must be considered.

K. Antimicrobial Stewardship

Antimicrobial stewardship is a critically important tool intended to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use. These consequences include drug toxicity, superinfection, emergence of bacterial resistance, and impact upon the human microbiome. **The Infectious Diseases Society of America recommends establishment of an antimicrobial stewardship team at all acute care facilities.** The core members of a stewardship team should include an infectious diseases physician and a clinical pharmacist with infectious diseases training. If possible, the addition of a clinical microbiologist, an information system specialist, an infection control professional, and a hospital epidemiologist would be

preferable. Key strategies for a stewardship team, as well as the individual prescriber, should include questions associated with the “Four Moments of Antibiotic Decision Making”: (1) Does this patient have an infection that requires antibiotics? (2) Have the appropriate cultures been ordered before starting antibiotics? (3) After a few days of empiric antibiotics have passed, can antibiotics be stopped? Can therapy be narrowed? Can therapy be switched from intravenous to oral? (4) What duration of antibiotic therapy is necessary for this patient’s diagnosis? Stewardship interventions centered upon one or more of the above questions have been demonstrated to decrease the risk of *C difficile* and *Candida* superinfection as well as attenuate the negative impact of antibiotics on the human microbiome.

Kadri SS et al. U.S. efforts to curb antibiotic resistance—are we saving lives? *N Engl J Med.* 2020;383:806. [PMID: 32846058]
Tamma PD et al. Rethinking how antibiotics are prescribed: incorporating the 4 moments of antibiotic decision making into clinical practice. *JAMA.* 2019;321:139. [PMID: 30589917]

HYPERSensitivity

► Penicillin Allergy

All penicillins are cross-sensitizing and cross-reacting. Skin tests using penicilloyl-polylysine and undegraded penicillin can identify most individuals with IgE-mediated reactions (hives, bronchospasm). In those patients with positive reaction to skin tests, the incidence of subsequent immediate severe reactions associated with penicillin administration is high. A history of a penicillin reaction in the past is often *not* reliable. Only a small proportion (less than 5%) of patients with a stated history of penicillin allergy experience an adverse reaction when challenged with the medication. The decision to administer penicillin or related medications (other beta-lactams) to patients with an allergic history depends on the severity of the reported reaction, the severity of the infection being treated, and the availability of alternative medications. For patients with a history of severe reaction (anaphylaxis), alternative medications should be used. In the rare situations when there is a strong indication for using penicillin (eg, syphilis in pregnancy) in allergic patients, desensitization can be performed. If the reaction is mild (nonurticarial rash), the patient may be rechallenged with penicillin or may be given another beta-lactam antibiotic.

Allergic reactions include anaphylaxis, serum sickness (urticaria, fever, joint swelling, angioedema 7–12 days after exposure), skin rashes, fever, interstitial nephritis, eosinophilia, hemolytic anemia, other hematologic disturbances, and vasculitis. The incidence of hypersensitivity to penicillin is estimated to be 1–5% among adults in the United States. Life-threatening anaphylactic reactions are very rare (0.05%). Ampicillin produces maculopapular skin rashes more frequently than other penicillins, but many ampicillin (and other beta-lactam) rashes are not

allergic in origin. The nonallergic ampicillin rash usually occurs after 3–4 days of therapy, is maculopapular, is more common in patients with coexisting viral illness (especially Epstein-Barr infection), and resolves with continued therapy. The maculopapular rash may or may not reappear with rechallenge. Beta-lactams can induce nephritis with primary tubular lesions associated with anti-basement membrane antibodies.

If the intradermal test described below is negative, desensitization is not necessary, and a full dose of the penicillin may be given. If the test is positive, alternative medications should be strongly considered. If that is not feasible, desensitization is necessary.

Patients with a history of allergy to penicillin are also at an increased risk for having a reaction to cephalosporins or carbapenems. A common approach to these patients is to assess the severity of the reaction. If an IgE-mediated reaction to penicillin can be excluded by history, a cephalosporin can be administered. When the history justifies concern about an immediate-type reaction, penicillin skin testing should be performed. If the test is negative, the cephalosporin or carbapenem can be given. If the test is positive, there is a 5–10% chance of cross reactivity with cephalosporins, and the decision whether to use cephalosporins depends on the availability of alternative agents and the severity of the infection. While carbapenems were considered highly cross reactive with penicillins, the cross reactivity appears to be minimal (1%).

IMMUNIZATION AGAINST INFECTIOUS DISEASES

RECOMMENDED IMMUNIZATION FOR ADULTS

Immunization is one of the most important tools (along with sanitation) used to prevent morbidity and mortality from infectious diseases. In general, the administration of most vaccinations induces a durable antibody response (**active immunity**). In contrast, **passive immunization** occurs when preformed antibodies are given (eg, immune globulin from pooled serum), resulting in temporary protection which is a less durable response. The two variants of active immunization are **live attenuated vaccines** (which are believed to result in an immunologic response more like natural infection), and **inactivated or killed vaccines**.

The schedule of vaccinations varies based on the risk of the disease being prevented by vaccination, whether a vaccine has been given previously, the immune status of the patient (probability of responding to vaccine) and safety of the vaccine (live versus killed product, as well as implications for the fetus in pregnant women). Recommendations for healthy adults as well as special populations based on medical conditions are summarized in Table 30–7, which can be accessed online at <https://www.cdc.gov/vaccines/schedules>.

1. Healthy Adults

Vaccination recommendations are made by the Advisory Committee on Immunization Practices (ACIP) of the US Centers for Disease Control and Prevention (Table 30–7). Characteristics of selected COVID-19 vaccines, as of March 2021, are presented in Table 30–8.

2. Pregnant Women

Given the uncertainty of risks to the fetus, vaccination during pregnancy is *generally avoided* with the following exceptions: tetanus (transfer of maternal antibodies across the placenta is important to prevent neonatal tetanus), diphtheria, and influenza. Live vaccines are avoided during pregnancy.

Influenza can be a serious infection if acquired in pregnancy, and *all pregnant women should be offered influenza (inactivated) vaccination*. The live attenuated (intranasal) influenza vaccine is *not recommended* during pregnancy.

3. HIV-Infected Adults

HIV-infected patients have impaired cellular and B cell responses. Inactivated or killed vaccinations can generally be given without any consequence, but the recipient may not be able to mount an adequate antibody response. Live or attenuated vaccines are generally avoided with some exceptions (ie, in patients with CD4⁺ T lymphocytes greater than 200 cells/mcL [$0.2 \times 10^9/L$]). Guidelines for vaccinating HIV-infected patients have been issued jointly by the Centers for Disease Control and Prevention, the US National Institutes of Health, and the HIV Medical Association of the Infectious Diseases Society of America. Timing of vaccination is important to optimize response. If possible, vaccination should be given early in the course of HIV disease or following immune reconstitution.

4. Hematopoietic Cell Transplant Recipients

Hematopoietic cell transplant (HCT) recipients have varying rates of immune reconstitution following transplantation, depending on (1) the type of chemotherapy or radiotherapy used pretransplant (in autologous HCT), (2) the preparative regimen used for the transplant, (3) whether graft-versus-host disease is present, and (4) the type of immunosuppression used posttransplantation (in allogeneic HCT). Vaccines may not work immediately in the posttransplant period. B cells may take 3–12 months to return to normal posttransplant, and naïve T cells that can respond to new antigens appear only 6–12 months posttransplant. B cells of posttransplant patients treated with rituximab may take up to 6 months to fully recover after the last dose of the medication. Vaccines are therefore administered 6–12 months following transplantation with a minimum of 1 month between doses to maximize the probability of response.

Table 30-7. Recommended adult immunization schedule—United States, 2021.**Recommended Adult Immunization Schedule by Age Group, United States, 2021**

Vaccine	19–26 years	27–49 years	50–64 years	≥65 years
Influenza inactivated (IIV) or Influenza recombinant (RIV4)		1 dose annually or		
Influenza live, attenuated (LAIV4)		1 dose annually or		
Tetanus, diphtheria, pertussis (Tdap or Td)		1 dose Tdap each pregnancy; 1 dose Td/Tdap for wound management (see notes) 1 dose Tdap, then Td or Tdap booster every 10 years		
Measles, mumps, rubella (MMR)		1 or 2 doses depending on indication (if born in 1957 or later)		
Varicella (VAR)	2 doses (if born in 1980 or later)		2 doses	
Zoster recombinant (RZV)			2 doses	
Human papillomavirus (HPV)	2 or 3 doses depending on age at initial vaccination or condition	27 through 45 years		
Pneumococcal conjugate (PCV13)		1 dose		1 dose
Pneumococcal polysaccharide (PPSV23)		1 or 2 doses depending on indication		1 dose
Hepatitis A (HepA)		2 or 3 doses depending on vaccine		
Hepatitis B (HepB)		2 or 3 doses depending on vaccine		
Meningococcal A, C, W, Y (MenACWY)		1 or 2 doses depending on indication, see notes for booster recommendations		
Meningococcal B (MenB)	19 through 23 years	2 or 3 doses depending on vaccine and indication, see notes for booster recommendations		
<i>Haemophilus influenzae</i> type b (Hib)		1 or 3 doses depending on indication		

Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of past infection

Recommended vaccination for adults with an additional risk factor or another indication

Recommended vaccination based on shared clinical decision-making

No recommendation/Not applicable

Recommended Adult Immunization Schedule by Medical Condition and Other Indications, United States, 2021

Vaccine	Pregnancy	Immuno-compromised (excluding HIV infection)	HIV infection CD4 count <200 mm ³ ≥200 mm ³	Asplenia, complement deficiencies	End-stage renal disease; or on hemodialysis	Heart or lung disease, alcoholism ¹	Chronic liver disease	Diabetes	Health care personnel ²	Men who have sex with men
IIV or RIV4 <i>or</i>						1 dose annually				
LAIV4		Not Recommended			Precaution				1 dose annually	
Tdap or Td	1 dose Tdap each pregnancy				1 dose Tdap, then Td or Tdap booster every 10 years					
MMR	Not Recommended*	Not Recommended				1 or 2 doses depending on indication				
VAR	Not Recommended*	Not Recommended				2 doses				
RZV					2 doses at age ≥50 years					
HPV	Not Recommended*	3 doses through age 26 years		2 or 3 doses through age 26 years depending on age at initial vaccination or condition						
PCV13					1 dose					
PPSV23					1, 2, or 3 doses depending on age and indication					
HepA					2 or 3 doses depending on vaccine					
HepB				2, 3, or 4 doses depending on vaccine or condition			<60 years			
							≥60 years			
MenACWY		1 or 2 doses depending on indication, see notes for booster recommendations								
MenB	Precaution		2 or 3 doses depending on vaccine and indication, see notes for booster recommendations							
Hib		3 doses HSCT ³ recipients only		1 dose						
<p>█ Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of past infection</p> <p>█ Recommended vaccination for adults with an additional risk factor or another indication</p> <p>█ Precaution—vaccination might be indicated if benefit of protection outweighs risk of adverse reaction</p> <p>█ Recommended vaccination based on shared clinical decision-making</p> <p>█ Not recommended/contraindicated—vaccine should not be administered.</p> <p>█ No recommendation/Not applicable</p>										
<p>*Vaccinate after pregnancy.</p> <p>¹Precaution for LAIV4 does not apply to alcoholism.</p> <p>²See notes for influenza; hepatitis B; measles, mumps, and rubella; and varicella vaccinations.</p> <p>³Hematopoietic stem cell transplant.</p>										

1. Precaution for LAIV4 does not apply to alcoholism. 2. See notes for influenza; hepatitis B; measles, mumps, and rubella; and varicella vaccinations. 3. Hematopoietic stem cell transplant.

(continued)

Table 30–7. Recommended adult immunization schedule—United States, 2021. (continued)**NOTES**

For vaccine recommendations for persons 18 years of age or younger, see the **Recommended Child/Adolescent Immunization Schedule**.

Additional Information**COVID-19 Vaccination**

ACIP recommends use of COVID-19 vaccines within the scope of the Emergency Use Authorization or Biologics License Application for the particular vaccine. Interim ACIP recommendations for the use of COVID-19 vaccines can be found at www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/covid-19.html.

Haemophilus influenzae type b vaccination**Special situations**

- Anatomical or functional asplenia (including sickle cell disease): 1 dose if previously did not receive Hib; if elective splenectomy, 1 dose, preferably at least 14 days before splenectomy
- Hematopoietic stem cell transplant (HSCT): 3-dose series 4 weeks apart starting 6–12 months after successful transplant, regardless of Hib vaccination history

Hepatitis A vaccination**Routine vaccination**

- Not at risk but want protection from hepatitis A (identification of risk factor not required): 2-dose series HepA (Havrix 6–12 months apart or Vaqta 6–18 months apart [minimum interval: 6 months] or 3-dose series HepA-HepB [Twinrix] at 0, 1, 6 months [minimum intervals: dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 5 months])

Special situations

- At risk for hepatitis A virus infection: 2-dose series HepA or 3-dose series HepA-HepB as above
 - Chronic liver disease (e.g., persons with hepatitis B, hepatitis C, cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, alanine aminotransferase [ALT] or aspartate aminotransferase [AST] level greater than twice the upper limit of normal)
 - HIV infection
 - Men who have sex with men
 - Injection or noninjection drug use
 - Persons experiencing homelessness
 - Work with hepatitis A virus in research laboratory or with nonhuman primates with hepatitis A virus infection
 - Travel in countries with high or intermediate endemic hepatitis A (HepA-HepB [Twinrix] may be administered on an accelerated schedule of 3 doses at 0, 7, and 21–30 days, followed by a booster dose at 12 months)
 - Close, personal contact with international adoptee (e.g., household or regular babysitting) in first 60 days after arrival from country with high or intermediate endemic hepatitis A (administer dose 1 as soon as adoption is planned, at least 2 weeks before adoptee's arrival)
 - Pregnancy if at risk for infection or severe outcome from infection during pregnancy
 - Settings for exposure, including health care settings targeting services to injection or noninjection drug users or group homes and nonresidential day care facilities for developmentally disabled persons (individual risk factor screening not required)

Hepatitis B vaccination**Routine vaccination**

- Not at risk but want protection from hepatitis B (identification of risk factor not required): 2- or 3-dose series (2-dose series Heplisav-B at least 4 weeks apart [2-dose series HepB only applies when 2 doses of Heplisav-B are used at least 4 weeks apart] or 3-dose series Engerix-B or Recombivax HB at 0, 1, 6 months [minimum intervals: dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 8 weeks / dose 1 to dose 3: 16 weeks]) or 3-dose series HepA-HepB (Twinrix at 0, 1, 6 months [minimum intervals: dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 5 months])

Special situations

- At risk for hepatitis B virus infection: 2-dose (Heplisav-B) or 3-dose (Engerix-B, Recombivax HB) series or 3-dose series HepA-HepB (Twinrix) as above
 - Chronic liver disease (e.g., persons with hepatitis C, cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, alanine aminotransferase [ALT] or aspartate aminotransferase [AST] level greater than twice upper limit of normal)
 - HIV infection
 - Sexual exposure risk (e.g., sex partners of hepatitis B surface antigen [HBsAg]-positive persons; sexually active persons not in mutually monogamous relationships; persons seeking evaluation or treatment for a sexually transmitted infection; men who have sex with men)
 - Current or recent injection drug use

-Percutaneous or mucosal risk for exposure to blood (e.g., household contacts of HBsAg-positive persons; residents and staff of facilities for developmentally disabled persons; health care and public safety personnel with reasonably anticipated risk for exposure to blood or blood-contaminated body fluids; hemodialysis, peritoneal dialysis, home dialysis, and predialysis patients; persons with diabetes mellitus age younger than 60 years, shared clinical decision-making for persons age 60 years or older)

-Incarcerated persons

-Travel in countries with high or intermediate endemic hepatitis B

-Pregnancy if at risk for infection or severe outcome from infection during pregnancy (Heplisav-B not currently recommended due to lack of safety data in pregnant women)

Human papillomavirus vaccination

Routine vaccination

- **HPV vaccination recommended for all persons through age 26 years:** 2- or 3-dose series depending on age at initial vaccination or condition:
 - Age 15 years or older at initial vaccination:** 3-dose series at 0, 1–2 months, 6 months (minimum intervals: dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 12 weeks / dose 1 to dose 3: 5 months; repeat dose if administered too soon)
 - Age 9–14 years at initial vaccination and received 1 dose or 2 doses less than 5 months apart:** 1 additional dose
 - Age 9–14 years at initial vaccination and received 2 doses at least 5 months apart:** HPV vaccination series complete, no additional dose needed
- **Interrupted schedules:** If vaccination schedule is interrupted, the series does not need to be restarted
- **No additional dose recommended after completing series with recommended dosing intervals using any HPV vaccine**

Shared clinical decision-making

- Some adults age 27–45 years: Based on shared clinical decision-making, 2- or 3-dose series as above

Special situations

- Age ranges recommended above for routine and catch-up vaccination or shared clinical decision-making also apply in special situations
 - Immunocompromising conditions, including HIV infection:** 3-dose series as above, regardless of age at initial vaccination
 - Pregnancy:** HPV vaccination not recommended until after pregnancy; no intervention needed if vaccinated while pregnant; pregnancy testing not needed before vaccination

Influenza vaccination

Routine vaccination

- **Persons age 6 months or older:** 1 dose any influenza vaccine appropriate for age and health status annually
- For additional guidance, see www.cdc.gov/flu/professionals/index.htm

Special situations

- **Egg allergy, hives only:** 1 dose any influenza vaccine appropriate for age and health status annually
- **Egg allergy—any symptom other than hives** (e.g., angioedema, respiratory distress): 1 dose any influenza vaccine appropriate for age and health status annually. If using an influenza vaccine other than RIV4 or cclIV4, administer in medical setting under supervision of health care provider who can recognize and manage severe allergic reactions.
- Severe allergic reactions to any vaccine can occur even in the absence of a history of previous allergic reaction. Therefore, all vaccine providers should be familiar with the office emergency plan and certified in cardiopulmonary resuscitation.
- A previous severe allergic reaction to any influenza vaccine is a contraindication to future receipt of the vaccine.
- **LAI4 should not be used** in persons with the following conditions or situations:
 - History of severe allergic reaction to any vaccine component (excluding egg) or to a previous dose of any influenza vaccine
 - Immunocompromised due to any cause (including medications and HIV infection)
 - Anatomic or functional asplenia
 - Close contacts or caregivers of severely immunosuppressed persons who require a protected environment
 - Pregnancy
 - Cranial CSF/oropharyngeal communications
 - Cochlear implant
 - Received influenza antiviral medications oseltamivir or zanamivir within the previous 48 hours, peramivir within the previous 5 days, or baloxavir within the previous 17 days
 - Adults 50 years or older
- **History of Guillain-Barré syndrome within 6 weeks after previous dose of influenza vaccine:** Generally, should not be vaccinated unless vaccination benefits outweigh risks for those at higher risk for severe complications from influenza

(continued)

Table 30–7. Recommended adult immunization schedule—United States, 2021. (continued)**Measles, mumps, and rubella vaccination****Routine vaccination**

- No evidence of immunity to measles, mumps, or rubella: 1 dose
 - Evidence of immunity: Born before 1957 (health care personnel, see below), documentation of receipt of MMR vaccine, laboratory evidence of immunity or disease (diagnosis of disease without laboratory confirmation is not evidence of immunity)

Special situations

- Pregnancy with no evidence of immunity to rubella: MMR contraindicated during pregnancy; after pregnancy (before discharge from health care facility), 1 dose
- Nonpregnant women of childbearing age with no evidence of immunity to rubella: 1 dose
- HIV infection with CD4 count ≥ 200 cells/mm 3 for at least 6 months and no evidence of immunity to measles, mumps, or rubella: 2-dose series at least 4 weeks apart; MMR contraindicated for HIV infection with CD4 count < 200 cells/mm 3
- Severe immunocompromising conditions: MMR contraindicated
- Students in postsecondary educational institutions, international travelers, and household or close, personal contacts of immunocompromised persons with no evidence of immunity to measles, mumps, or rubella: 2-dose series at least 4 weeks apart if previously did not receive any doses of MMR or 1 dose if previously received 1 dose MMR
- Health care personnel:
 - Born in 1957 or later with no evidence of immunity to measles, mumps, or rubella: 2-dose series at least 4 weeks apart for measles or mumps or at least 1 dose for rubella
 - Born before 1957 with no evidence of immunity to measles, mumps, or rubella: Consider 2-dose series at least 4 weeks apart for measles or mumps or 1 dose for rubella

Meningococcal vaccination**Special situations for MenACWY**

- Anatomical or functional asplenia (including sickle cell disease), HIV infection, persistent complement component deficiency, complement inhibitor (e.g., eculizumab, ravulizumab) use: 2-dose series MenACWY-D (Menactra, Menevo or MenQuadfi) at least 8 weeks apart and revaccinate every 5 years if risk remains
- Travel in countries with hyperendemic or epidemic meningococcal disease, microbiologists routinely exposed to *Neisseria meningitidis*: 1 dose MenACWY (Menactra, Menevo or MenQuadfi) and revaccinate every 5 years if risk remains
- First-year college students who live in residential housing (if not previously vaccinated at age 16 years or older) and military recruits: 1 dose MenACWY (Menactra, Menevo or MenQuadfi)
- For MenACWY booster dose recommendations for groups listed under "Special situations" and in an outbreak setting (e.g., in community or organizational settings and among men who have sex with men) and additional meningococcal vaccination information, see www.cdc.gov/mmwr/volumes/69/rr/rr6909a1.htm

Shared clinical decision-making for MenB

- Adolescents and young adults age 16–23 years (age 16–18 years preferred) not at increased risk for meningococcal disease: Based on shared clinical decision-making, 2-dose series MenB-4C (Bexsero) at least 1 month apart or 2-dose series MenB-FHbp (Trumenba) at 0, 6 months (if dose 2 was administered less than 6 months after dose 1, administer dose 3 at least 4 months after dose 2); MenB-4C and MenB-FHbp are not interchangeable (use same product for all doses in series)

Special situations for MenB

- Anatomical or functional asplenia (including sickle cell disease), persistent complement component deficiency, complement inhibitor (e.g., eculizumab, ravulizumab) use, microbiologists routinely exposed to *Neisseria meningitidis*: 2-dose primary series MenB-4C (Bexsero) at least one month apart
- MenB-4C (Bexsero) at least 1 month apart or 3-dose primary series MenB-FHbp (Trumenba) at 0, 1–2, 6 months (if dose 2 was administered at least 6 months after dose 1, dose 3 not needed); MenB-4C and MenB-FHbp are not interchangeable (use same product for all doses in series); 1 dose MenB booster 1 year after primary series and revaccinate every 2–3 years if risk remains
- Pregnancy:** Delay MenB until after pregnancy unless at increased risk and vaccination benefits outweigh potential risks
- For MenB booster dose recommendations for groups listed under "Special situations" and in an outbreak setting (e.g., in community or organizational settings and among men who have sex with men) and additional meningococcal vaccination information, see www.cdc.gov/mmwr/volumes/69/rr/rr6909a1.htm

Pneumococcal vaccination**Routine vaccination**

- Age 65 years or older (immunocompetent—see www.cdc.gov/mmwr/volumes/68/wr/mm6846a5.htm?s_cid=mm6846a5_w): 1 dose PPSV23
 - If PPSV23 was administered prior to age 65 years, administer 1 dose PPSV23 at least 5 years after previous dose

Shared clinical decision-making

- Age 65 years or older (immunocompetent): 1 dose PCV13 based on shared clinical decision-making if previously not administered.
 - PCV13 and PPSV23 should not be administered during the same visit
 - If both PCV13 and PPSV23 are to be administered, PCV13 should be administered first
 - PCV13 and PPSV23 should be administered at least 1 year apart

Special situations

(www.cdc.gov/mmwr/preview/mmwrhtml/mm6140a4.htm)

- Age 19–64 years with chronic medical conditions (chronic heart [excluding hypertension], lung, or liver disease, diabetes), alcoholism, or cigarette smoking: 1 dose PPSV23
- Age 19 years or older with immunocompromising conditions (congenital or acquired immunodeficiency [including B- and T-lymphocyte deficiency, complement deficiencies, phagocytic disorders, HIV infection], chronic renal failure, nephrotic syndrome, leukemia, lymphoma, Hodgkin disease, generalized malignancy, iatrogenic immunosuppression [e.g., drug or radiation therapy], solid organ transplant, multiple myeloma] or anatomical or functional asplenia [including sickle cell disease and other hemoglobinopathies]): 1 dose PCV13 followed by 1 dose PPSV23 at least 8 weeks later, then another dose PPSV23 at least 5 years after previous PPSV23; at age 65 years or older, administer 1 dose PPSV23 at least 5 years after most recent PPSV23 (note: only 1 dose PPSV23 recommended at age 65 years or older)
- Age 19 years or older with cerebrospinal fluid leak or cochlear implant: 1 dose PCV13 followed by 1 dose PPSV23 at least 8 weeks later; at age 65 years or older, administer another dose PPSV23 at least 5 years after PPSV23 (note: only 1 dose PPSV23 recommended at age 65 years or older)

Tetanus, diphtheria, and pertussis vaccination

Routine vaccination

- Previously did not receive Tdap at or after age 11 years: 1 dose Tdap, then Td or Tdap every 10 years

Special situations

- Previously did not receive primary vaccination series for tetanus, diphtheria, or pertussis: At least 1 dose Tdap followed by 1 dose Td or Tdap at least 4 weeks after Tdap and another dose Td or Tdap 6–12 months after last Td or Tdap (Tdap can be substituted for any Td dose, but preferred as first dose), Td or Tdap every 10 years thereafter
- Pregnancy: 1 dose Tdap during each pregnancy, preferably in early part of gestational weeks 27–36
- Wound management: Persons with 3 or more doses of tetanus-toxoid-containing vaccine: For clean and minor wounds, administer Tdap or Td if more than 10 years since last dose of tetanus-toxoid-containing vaccine; for all other wounds, administer Tdap or Td if more than 5 years since last dose of tetanus-toxoid-containing vaccine. Tdap is preferred for persons who have not previously received Tdap or whose Tdap history is unknown. If a tetanus-toxoid-containing vaccine is indicated for a pregnant woman, use Tdap. For detailed information, see www.cdc.gov/mmwr/volumes/69/wr/mm6903a5.htm

Varicella vaccination

Routine vaccination

- No evidence of immunity to varicella: 2-dose series 4–8 weeks apart if previously did not receive varicella-containing vaccine (VAR or MMRV [measles-mumps-rubella-varicella vaccine] for children); if previously received 1 dose varicella-containing vaccine, 1 dose at least 4 weeks after first dose
 - Evidence of immunity: U.S.-born before 1980 (except for pregnant women and health care personnel [see below]), documentation of 2 doses varicella-containing vaccine at least 4 weeks apart, diagnosis or verification of history of varicella or herpes zoster by a health care provider, laboratory evidence of immunity or disease

Special situations

- Pregnancy with no evidence of immunity to varicella: VAR contraindicated during pregnancy; after pregnancy (before discharge from health care facility), 1 dose if previously received 1 dose varicella-containing vaccine or dose 1 of 2-dose series (dose 2: 4–8 weeks later) if previously did not receive any varicella-containing vaccine, regardless of whether U.S.-born before 1980
- Health care personnel with no evidence of immunity to varicella: 1 dose if previously received 1 dose varicella-containing vaccine; 2-dose series 4–8 weeks apart if previously did not receive any varicella-containing vaccine, regardless of whether U.S.-born before 1980
- HIV infection with CD4 count ≥ 200 cells/mm 3 with no evidence of immunity: Vaccination may be considered (2 doses 3 months apart); VAR contraindicated for HIV infection with CD4 count < 200 cells/mm 3
- Severe immunocompromising conditions: VAR contraindicated

Zoster vaccination

Routine vaccination

- Age 50 years or older: 2-dose series RZV (Shingrix) 2–6 months apart (minimum interval: 4 weeks; repeat dose if administered too soon), regardless of previous herpes zoster or history of zoster vaccine live (ZVL, Zostavax) vaccination (administer RZV at least 2 months after ZVL)

Special situations

- Pregnancy: Consider delaying RZV until after pregnancy if RZV is otherwise indicated.
- Severe immunocompromising conditions (including HIV infection with CD4 count < 200 cells/mm 3): Recommended use of RZV under review

Table 30–8. Selected COVID-19 vaccines and adverse effects.¹

Vaccine (Type)	Dosing	Storage	Adverse Effects
AstraZeneca/University of Oxford (adenovirus vector)	Two doses, 4–12 weeks apart	Refrigerator (2–8°C)	Local: at site of injection Systemic: fevers, chills, myalgias, fatigue, headache
Janssen/Johnson & Johnson (adenovirus vector)	One dose	Refrigerator (2–8°C)	Local: at site of injection Systemic: fevers, chills, myalgias, fatigue, headache
Moderna (mRNA)	Two doses, 4 weeks apart	Freezer (−20°C) then refrigerator (2–8°C) for up to 30 days	Local: at site of injection Systemic: fevers, chills, myalgias, fatigue, headache Severe allergies: anaphylaxis in 2.5/1 million
Novavax (recombinant protein)	Two doses, 3 weeks apart	Refrigerator (2–8°C)	Local: at site of injection Systemic: fevers, chills, myalgias, fatigue, headache
Pfizer/BioNTech (mRNA)	Two doses, 3 weeks apart	Ultracold freezer (−70°C) then freezer (−20°C for up to 2 weeks) then refrigerator (2–8°C) for up to 5 days	Local: at site of injection Systemic: fevers, chills, myalgias, fatigue, headache Severe allergies: anaphylaxis in 11/1 million

¹Updated as of March 2021; see also Chapter 32, SARS-CoV-2 section.

5. Solid Organ Transplant Recipients

Solid organ transplant recipients demonstrate a broad spectrum of immunosuppression, depending on the reason for and type of organ transplantation and the nature of the immunosuppression (including T-cell-depleting agents during treatment of organ rejection). These factors affect the propensity for infection posttransplantation and the ability to develop antibody responses to vaccination. In many cases, the time between placing a patient on a transplant list and undergoing the transplantation takes months or years. Providers should take this opportunity to ensure that indicated vaccines are given during this pretransplant period to optimize antibody responses. If this is not possible, most experts give vaccines 3–6 months following transplantation. Live vaccines are contraindicated in the post-transplant period.

RECOMMENDED IMMUNIZATIONS FOR TRAVELERS

Individuals traveling to other countries frequently require immunizations in addition to those routinely recommended and may benefit from chemoprophylaxis against various diseases. Vaccinations against yellow fever and meningococcus are the only ones required by certain countries. These and other travel-specific vaccines are listed at <http://wwwnc.cdc.gov/travel/destinations/list>.

Various vaccines can be given simultaneously at different sites. Some, such as cholera, plague, and typhoid vaccine, cause significant discomfort and are best given at

different times. In general, live attenuated vaccines (measles, mumps, rubella, yellow fever, and oral typhoid vaccine) should not be given to immunosuppressed individuals or household members of immunosuppressed people or to pregnant women. Immunoglobulin should not be given for 3 months before or at least 2 weeks after live virus vaccines, because it may attenuate the antibody response.

Chemoprophylaxis of malaria is discussed in Chapter 35.

VACCINE SAFETY

Most vaccines are safe to administer. In general, it is recommended that the use of live vaccines be avoided in immunocompromised patients, including pregnant women. Vaccines are generally not contraindicated in the following situations: mild, acute illness with low-grade fevers (less than 40.5°C); concurrent antibiotic therapy; soreness or redness at the site; and family history of adverse reactions to vaccinations. Absolute contraindications to vaccines are rare (Table 30–9).

Centers for Disease Control and Prevention (CDC). Adult immunization schedules—United States, 2021. <https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html>

Centers for Disease Control and Prevention (CDC). Health Information for International Travel. <https://wwwnc.cdc.gov/travel/page/yellowbook-home>

Centers for Disease Control and Prevention (CDC). Vaccine safety. <https://www.cdc.gov/vaccinesafety/index.html>

Danziger-Isakov L et al. Vaccination of solid organ transplant candidates and recipients: guidelines from the American society of transplantation infectious diseases community of practice. Clin Transplant. 2019;33:e13563. [PMID: 31002409]

Table 30–9. Adverse effects and contraindications to commonly used vaccines in adults (listed in alphabetical order).

Vaccine	Adverse Effects	Contraindications ¹
<i>Haemophilus influenzae</i> type b (Hib)	Minimal Consist mainly of pain at the injection site	Any severe allergic reaction (eg, anaphylaxis) after a previous dose or to a vaccine component.
Hepatitis A	Minimal Consist mainly of pain at the injection site	Any severe allergic reaction (eg, anaphylaxis) after a previous dose or to a vaccine component.
Hepatitis B	Minimal Consist mainly of pain at the injection site	Any severe allergic reaction (eg, anaphylaxis) after a previous dose or to a vaccine component.
Human papillomavirus	Minimal Consist mainly of mild to moderate localized pain, erythema, swelling Systemic reactions, mainly fever, seen in 4% of recipients	Any severe allergic reaction (eg, anaphylaxis) after a previous dose or to a vaccine component.
Influenza (intramuscular inactivated and intranasal live attenuated vaccines)	Intramuscular, inactivated vaccine: Local reactions (erythema and tenderness) at the site of injection are common, but fevers, chills, and malaise (which last in any case only 2–3 days) are rare. Either inactivated or live attenuated vaccine: A potential association between Guillain-Barré syndrome (3000–6000 cases per year in the United States, usually following respiratory infections) and vaccination with intramuscular, inactivated influenza vaccine has been reported (possibly, 1–2 persons per million persons vaccinated), but this rate is lower than the risk of the syndrome developing after influenza itself (given that approximately 750 persons per million adults are hospitalized annually with influenza, and many more cases remain as outpatients). Influenza vaccination may be associated with multiple false-positive serologic tests to HIV, HTLV-1, and hepatitis C, but it is self-limited, lasting 2–5 months.	Contraindication to both inactivated and live attenuated vaccine: History of Guillain-Barré syndrome, especially within 6 weeks of receiving a previous influenza vaccine. Any severe allergic reaction (eg, anaphylaxis) after a previous dose or to a vaccine component, including egg protein. ² Intranasal, live attenuated vaccine [FluMist] should not be used in: <ul style="list-style-type: none">• People 50 years of age and over• Immunosuppressed individuals and those on immunosuppressive therapy• Household members of immunosuppressed individuals• Health care workers, or others with close contact with immunosuppressed persons• Presence of reactive airway disease (eg, asthma) or chronic underlying metabolic (eg, kidney), pulmonary, or heart diseases (use intramuscular inactivated vaccine)• Pregnancy³ It is recommended that salicylates should be avoided for 6 weeks following vaccination (to prevent Reye syndrome).
Measles, mumps, and rubella (MMR) ⁴	Fever will develop in about 5–15% of unimmunized individuals, and a mild rash will develop in about 5% 5–12 days after vaccination. Fever and rash are self-limited, lasting only 2–3 days. Local swelling and induration are particularly common in individuals previously vaccinated with inactivated vaccine.	Pregnancy ⁵ Known severe immunodeficiency (eg, from hematologic and solid cancers, receipt of chemotherapy, congenital immunodeficiency, long-term immunosuppressive therapy [eg, > 2 weeks of prednisone 20 mg daily or higher]), other disease- or therapy-related immune suppression, or patients with HIV infection who are severely immunocompromised. May be used in asymptomatic HIV-infected individuals whose CD4 count is > 200/mcL ($0.2 \times 10^9/L$). Severe allergic reaction (eg, anaphylaxis) to a previous dose or to a vaccine component (eg, neomycin or to related agents such as streptomycin).

(continued)

Table 30–9. Adverse effects and contraindications to commonly used vaccines in adults (listed in alphabetical order). (continued)

Vaccine	Adverse Effects	Contraindications ¹
Meningococcal, oligosaccharide conjugate; (MCV4 or MenACWY [Menactra, Meneveo]; meningococcal polysaccharide conjugate MPSV4 [Menomune]); meningococcal group B, recombinant (MenB [Bexsero, Trumenba])	Minor reactions (fever, redness, swelling, erythema, pain) occur slightly more commonly with MCV4. Major reactions are rare. A potential association between Guillain-Barré syndrome (3000–6000 cases per year in the United States, usually following respiratory infections) and vaccination with MCV4 has been reported, but current recommendations favor continued use of MCV4, since the benefits of preventing the serious consequences of meningococcal infection outweigh the theoretical risk of Guillain-Barré syndrome.	Any severe allergic reaction (eg, anaphylaxis) to a previous dose or to a vaccine component (eg, persons with history of adverse reaction to diphtheria toxoid should not receive meningococcal oligosaccharide conjugate and polysaccharide conjugate vaccines since the protein conjugate used in them is diphtheria toxoid).
Pneumococcal conjugate (PCV13 [Prevnar]); Pneumococcal polysaccharide (PPSV23) [Pneumovax])	Mild local reactions (erythema and tenderness) occur in up to 50% of recipients, but systemic reactions are uncommon. Similarly, revaccination at least 5 years after initial vaccination is associated with mild self-limited local but not systemic reactions.	Any severe allergic reaction (eg, anaphylaxis) after a previous dose or to a vaccine component (eg, for PCV13 to any vaccine containing diphtheria toxoid).
Tetanus, diphtheria, and pertussis (DTP, Tdap); tetanus, diphtheria (Td)	Minimal Consist mainly of pain at the injection site	Any severe allergic reaction (eg, anaphylaxis) after a previous dose or to a vaccine component. For pertussis-containing vaccines: any history of unexplained encephalopathy (eg, coma, decreased level of consciousness, or prolonged seizures) within 7 days of administration of a previous dose of Tdap or diphtheria and tetanus toxoids and pertussis (DTP) or diphtheria and tetanus toxoids and acellular pertussis (Tdap) vaccine.
Varicella	Can occur as late as 4–6 weeks after vaccination. Tenderness and erythema at the injection site are seen in 25%, fever in 10–15%, and a localized maculopapular or vesicular rash in 5%; a diffuse rash, usually with five or fewer vesicular lesions, develops in a smaller percentage. Spread of virus from vaccinees to susceptible individuals is possible, but the risk of such transmission even to immunocompromised patients is small, and disease, when it develops, is mild and treatable with acyclovir.	Known severe immunodeficiency (eg, from hematologic and solid cancers, receipt of chemotherapy, congenital immunodeficiency, long-term immunosuppressive therapy [eg, > 2 weeks of prednisone 20 mg daily or higher; other immunosuppressive medications], other disease- or therapy-related immune suppression, or patients with HIV infection who are severely immunocompromised). Pregnancy. Severe allergic reaction (eg, anaphylaxis) after a previous dose or to a vaccine component (eg, neomycin). For theoretic reasons, it is recommended that salicylates should be avoided for 6 weeks following vaccination (to prevent potential for Reye syndrome).

Zoster	Mild and limited to local reactions Although it is theoretically possible to transmit the virus to susceptible contacts, no such cases have been reported.	Known severe immunodeficiency (eg, from hematologic and solid cancers, receipt of chemotherapy, congenital immunodeficiency, long-term immunosuppressive therapy [eg, > 2 weeks of prednisone 20 mg daily or higher; other immunosuppressive medications], other disease- or therapy-related immune suppression, or patients with HIV infection who are severely immunocompromised. May be used in asymptomatic HIV-infected individuals whose CD4 count is > 200/mcL [$0.2 \times 10^9/L$]). Pregnancy. Any severe allergic reaction (eg, anaphylaxis) after a previous dose or to a vaccine component (eg, gelatin or neomycin).
--------	---	--

¹Adapted from Centers for Disease Control and Prevention. Contraindications and precautions to commonly used vaccines in adults. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices. <https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html>, accessed March 12, 2021; and from Hamborsky J et al (editors). Appendix A. Epidemiology and prevention of vaccine preventable diseases. 13th edition. Washington, DC, Public Health Foundation, 2015. Available at www.cdc.gov/vaccines/pubs/pinkbook/index.html.

²The vaccine has typically been prepared using embryonated chicken eggs. However, a new vaccine using mammalian cell culture is now FDA approved.

³The inactivated influenza vaccine can be given during any trimester.

⁴MMR vaccine can be safely given to patients with a history of egg allergy even when severe.

⁵Although vaccination of pregnant women is *not* recommended, with the currently available RA27/3 vaccine strain, the congenital rubella syndrome does not occur in the offspring of those inadvertently vaccinated during pregnancy or within 3 months before conception.

Freedman MS et al. Advisory Committee on Immunization Practices recommended immunization schedule for adults aged 19 years or older—United States, 2021. MMWR Morb Mortal Wkly Rep. 2021;70:193. [PMID: 33571173]

Grohskopf LA et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices—United States, 2019–20 influenza season. MMWR Recomm Rep. 2019;68:1. [PMID: 31441906]

Leidner AJ et al. Cost-effectiveness of adult vaccinations: a systematic review. Vaccine. 2019;37:226. [PMID: 30527660]
Paules CI et al. Chasing seasonal influenza—the need for a universal influenza vaccine. N Engl J Med. 2018;378:7. [PMID: 29185857]

HIV Infection & AIDS

Mitchell H. Katz, MD

31



ESSENTIALS OF DIAGNOSIS

- ▶ Modes of transmission: sexual contact with an infected person, parenteral exposure to infected blood (transfusion or needle sharing), perinatal exposure.
- ▶ Prominent systemic complaints: sweats, diarrhea, weight loss, and wasting.
- ▶ Opportunistic infections due to diminished cellular immunity—often life-threatening.
- ▶ Aggressive cancers, particularly non-Hodgkin lymphoma.
- ▶ Neurologic manifestations, including dementia, aseptic meningitis, and neuropathy.

► General Considerations

The Centers for Disease Control and Prevention (CDC) AIDS case definition (Table 31–1) includes opportunistic infections and malignancies that rarely occur in the absence of severe immunodeficiency (eg, *Pneumocystis pneumonia*, central nervous system lymphoma). It also classifies persons as having AIDS if they have positive HIV serology and certain infections and malignancies that can occur in immunocompetent hosts but that are more common among persons infected with HIV (pulmonary tuberculosis, invasive cervical cancer). Several nonspecific conditions, including dementia and wasting (documented weight loss)—in the presence of a positive HIV serology—are considered AIDS. The definition includes criteria for both definitive and presumptive diagnoses of certain infections and malignancies. Finally, persons with positive HIV serology who have ever had a CD4 lymphocyte count below 200 cells/mcL or a CD4 lymphocyte percentage below 14% are considered to have AIDS. Inclusion of persons with low CD4 counts as AIDS cases reflects the recognition that immunodeficiency is the defining characteristic of AIDS. The choice of a cutoff point at 200 cells/mcL is supported by several cohort studies showing that AIDS will develop within 3 years in over 80% of persons with counts below this level in the absence of effective antiretroviral

therapy. The prognosis of persons with HIV/AIDS has dramatically improved due to the development of effective antiretroviral treatment. One consequence is that fewer persons with HIV ever develop an infection or malignancy or have a low enough CD4 count to classify them as having AIDS, which means that the CDC definition has become a less useful measure of the impact of HIV/AIDS in the United States. Conversely, persons in whom AIDS had been diagnosed based on a serious opportunistic infection, malignancy, or immunodeficiency may now be markedly healthier, with high CD4 counts, due to the use of antiretroviral treatment. Therefore, the Social Security Administration as well as most social service agencies focus on functional assessment for determining eligibility for benefits rather than the simple presence or absence of an AIDS-defining illness.

► Epidemiology

The modes of transmission of HIV are similar to those of hepatitis B, in particular with respect to sexual, parenteral, and vertical transmission. Although certain sexual practices (eg, receptive anal intercourse) are significantly riskier than other sexual practices (eg, oral sex), it is difficult to quantify per-contact risks. The reason is that studies of sexual transmission of HIV show that most people at risk for HIV infection engage in a variety of sexual practices and have sex with multiple persons, only some of whom may actually be HIV infected. Thus, it is difficult to determine which practice with which person actually resulted in HIV transmission.

Nonetheless, the best available estimates indicate that the risk of HIV transmission with receptive anal intercourse is between 1:100 and 1:30, with insertive anal intercourse 1:1000, with receptive vaginal intercourse 1:1000, with insertive vaginal intercourse 1:10,000, and with receptive fellatio with ejaculation 1:1000. The per-contact risk of HIV transmission with other behaviors, including receptive fellatio without ejaculation, insertive fellatio, and cunnilingus, is not known.

A number of cofactors are known to increase the risk of HIV transmission during a given encounter, including the presence of ulcerative or inflammatory sexually transmitted diseases, trauma, menses, and lack of male circumcision.

Table 31–1. CDC AIDS case definition for surveillance of adults and adolescents.

Definitive AIDS Diagnoses (with or without laboratory evidence of HIV infection)
1. Candidiasis of the esophagus, trachea, bronchi, or lungs.
2. Cryptococcosis, extrapulmonary.
3. Cryptosporidiosis with diarrhea persisting > 1 month.
4. Cytomegalovirus disease of an organ other than liver, spleen, or lymph nodes.
5. Herpes simplex virus infection causing a mucocutaneous ulcer that persists > 1 month; or bronchitis, pneumonitis, or esophagitis of any duration.
6. Kaposi sarcoma in a patient < 60 years of age.
7. Lymphoma of the brain (primary) in a patient < 60 years of age.
8. <i>Mycobacterium avium</i> complex or <i>Mycobacterium kansasii</i> disease, disseminated (at a site other than or in addition to lungs, skin, or cervical or hilar lymph nodes).
9. <i>Pneumocystis jirovecii</i> pneumonia.
10. Progressive multifocal leukoencephalopathy.
11. Toxoplasmosis of the brain.
Definitive AIDS Diagnoses (with laboratory evidence of HIV infection)
1. Coccidioidomycosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes).
2. HIV encephalopathy.
3. Histoplasmosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes).
4. Isosporiasis with diarrhea persisting > 1 month.
5. Kaposi sarcoma at any age.
6. Lymphoma of the brain (primary) at any age.
7. Other non-Hodgkin lymphoma of B cell or unknown immunologic phenotype.
8. Any mycobacterial disease caused by mycobacteria other than <i>Mycobacterium tuberculosis</i> , disseminated (at a site other than or in addition to lungs, skin, or cervical or hilar lymph nodes).
9. Disease caused by extrapulmonary <i>M tuberculosis</i> .
10. <i>Salmonella</i> (nontyphoid) septicemia, recurrent.
11. HIV wasting syndrome.
12. CD4 lymphocyte count < 200 cells/mcL or a CD4 lymphocyte percentage < 14%.
13. Pulmonary tuberculosis.
14. Recurrent pneumonia.
15. Invasive cervical cancer.
Presumptive AIDS Diagnoses (with laboratory evidence of HIV infection)
1. Candidiasis of esophagus: (a) recent onset of retrosternal pain on swallowing; and (b) oral candidiasis.
2. Cytomegalovirus retinitis. A characteristic appearance on serial ophthalmoscopic examinations.
3. Mycobacteriosis. Specimen from stool or normally sterile body fluids or tissue from a site other than lungs, skin, or cervical or hilar lymph nodes, showing acid-fast bacilli of a species not identified by culture.
4. Kaposi sarcoma. Erythematous or violaceous plaque-like lesion on skin or mucous membrane.
5. <i>Pneumocystis jirovecii</i> pneumonia: (a) a history of dyspnea on exertion or nonproductive cough of recent onset (within the past 3 months); and (b) chest film evidence of diffuse bilateral interstitial infiltrates or gallium scan evidence of diffuse bilateral pulmonary disease; and (c) arterial blood gas analysis showing an arterial oxygen partial pressure < 70 mm Hg or a low respiratory diffusing capacity < 80% of predicted values or an increase in the alveolar-arterial oxygen tension gradient; and (d) no evidence of a bacterial pneumonia.
6. Toxoplasmosis of the brain: (a) recent onset of a focal neurologic abnormality consistent with intracranial disease or a reduced level of consciousness; and (b) brain imaging evidence of a lesion having a mass effect or the radiographic appearance of which is enhanced by injection of contrast medium; and (c) serum antibody to toxoplasmosis or successful response to therapy for toxoplasmosis.
7. Recurrent pneumonia: (a) more than one episode in a 1-year period; and (b) acute pneumonia (new symptoms, signs, or radiologic evidence not present earlier) diagnosed on clinical or radiologic grounds by the patient's clinician.
8. Pulmonary tuberculosis: (a) apical or miliary infiltrates and (b) radiographic and clinical response to antituberculous therapy.

The risk of acquiring HIV infection from a needlestick with infected blood is approximately 1:300. Factors known to increase the risk of transmission include depth of penetration, hollow bore needles, visible blood on the needle, and advanced stage of disease in the source. The risk of HIV transmission from a mucosal splash with infected blood is unknown but is assumed to be significantly lower.

The risk of acquiring HIV infection from illicit drug use with sharing of needles from an HIV-infected source is estimated to be 1:150. Use of clean needles markedly decreases the chance of HIV transmission, but does not eliminate it if other drug paraphernalia are shared (eg, cookers).

When blood transfusion from an HIV-infected donor occurs, the risk of transmission is 95%. Fortunately, since 1985, blood donor screening has been universally practiced in the United States. Also, persons who have recently engaged in unsafe behaviors (eg, sex with a person at risk for HIV, injection drug use) are not allowed to donate. This essentially eliminates donations from persons who are HIV infected but have not yet developed antibodies (ie, persons in the “window” period). HIV antigen and viral load testing have been added to the screening of blood to further lower the chance of HIV transmission. With these precautions, the chance of HIV transmission with receipt of blood transfusion in the United States is about 1:1,000,000.

Between 13% and 40% of children born to HIV-infected mothers contract HIV infection when the mother has not received treatment or when the child has not received perinatal HIV prophylaxis. The risk is higher with vaginal than with cesarean delivery, higher among mothers with high viral loads, and higher among those who breastfeed their children. The combination of prenatal HIV testing and counseling, antiretroviral treatment for infected mothers during pregnancy and for the infant immediately after birth, scheduled cesarean delivery if the mother has a viral load of greater than 1000 copies/mL, and avoidance of breastfeeding has reduced the rate of perinatal transmission of HIV to less than 2% in the United States and Europe.

HIV has not been shown to be transmitted by respiratory droplet spread, by vectors such as mosquitoes, or by casual nonsexual contact. Saliva, sweat, stool, and tears are not considered infectious fluids.

There are an estimated 1.2 million adults and adolescents in the United States living with HIV, 14% of whom are undiagnosed. Young people (age 13–24) are the most likely to not know they are infected. In 2018, 37,968 Americans were newly diagnosed with HIV infection; 79% men (30,166), 19% women (7189), and 2% (613) transgender and nonbinary individuals. Men who had sex with men accounted for 665 of the new diagnoses (24,993), and among them, Black and Latino men accounted for 38% and 31% of new infections, respectively. Heterosexual contacts accounted for 24% (9008) of new HIV diagnoses, and injection drug users (including men who have sex with men and use injection drugs) accounted for 10% (3864) of new HIV diagnoses. Among persons living with HIV in the United States, the prevalence of infection in the minority community was staggeringly higher. The rate of infection per 100,000 people was 1034 for Blacks, 666 for persons of multiple races, 386 for Latinos, compared to 154 among Whites.

In general, the progression of HIV-related illness is similar in men and women. However, there are some important differences. Women are at risk for gynecologic complications of HIV, including recurrent candidal vaginitis, pelvic inflammatory disease, and cervical dysplasia and carcinoma. Violence directed against women, pregnancy, and frequent occurrence of drug use and poverty all complicate the treatment of HIV-infected women.

Worldwide there are an estimated 37.9 million persons infected with HIV, with heterosexual spread being the most common mode of transmission for men and women. The reason for the greater risk for transmission with heterosexual intercourse in Africa and Asia than in the United States may relate to cofactors such as general health status, the presence of genital ulcers, relative lack of male circumcision, the number of sexual partners, and different HIV serotypes. It was estimated that in 2018, 76% of Americans living with HIV received some HIV care and 65% were virally suppressed.

Centers for Disease Control and Prevention. *HIV Surveillance Report, 2018 (Updated)*; vol.31. <http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html>. Published May 2020.

US Department of Health and Human Services. HIV Basics. <https://www.hiv.gov/hiv-basics>

World Health Organization. Number of people (all ages) living with HIV: estimates by WHO region. Updated 2019. https://www.who.int/gho/hiv/epidemic_status/cases_all_text/en/

World Health Organization. Recommended population size estimates of men who have sex with men. 2020 Nov 30. <https://www.who.int/publications/i/item/9789240015357>

► Pathophysiology

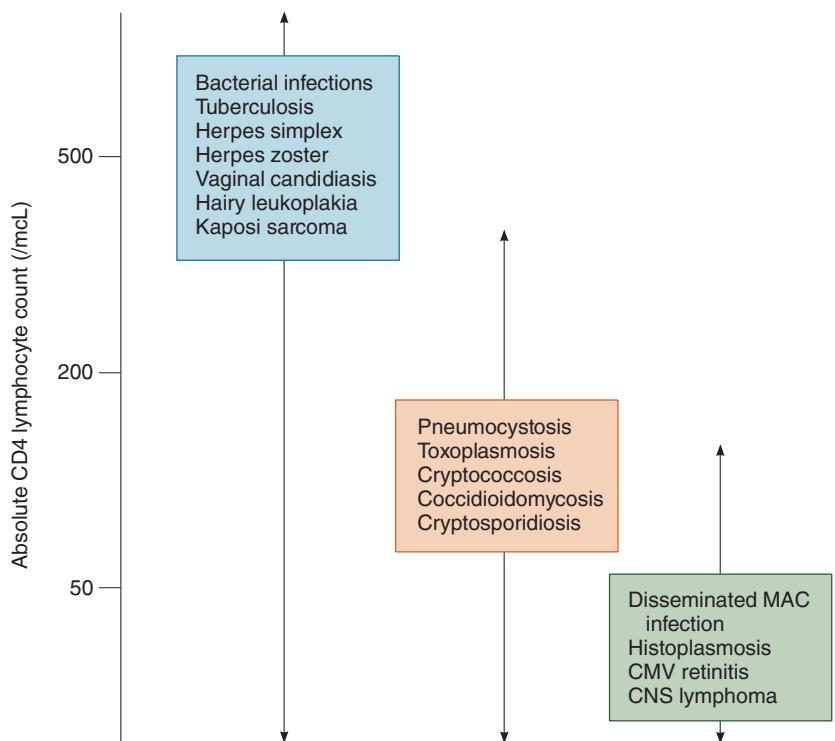
Clinically, the syndromes caused by HIV infection are usually explicable by one of three known mechanisms: immunodeficiency, autoimmunity, and allergic and hypersensitivity reactions.

A. Immunodeficiency

Immunodeficiency is a direct result of the effects of HIV upon immune cells as well as the indirect impact of a generalized state of inflammation and immune activation due to chronic viral infection. A spectrum of infections and neoplasms is seen, as in other congenital or acquired immunodeficiency states. Two remarkable features of HIV immunodeficiency are the low incidence of certain infections such as listeriosis and aspergillosis and the frequent occurrence of certain neoplasms such as lymphoma or Kaposi sarcoma. This latter complication has been seen primarily in men who have sex with men (MSM) or in bisexual men, and its incidence steadily declined through the first 15 years of the epidemic. A herpesvirus (KSHV or HHV-8) is the cause of Kaposi sarcoma.

B. Autoimmunity/Allergic and Hypersensitivity Reactions

Autoimmunity can occur as a result of disordered cellular immune function or B lymphocyte dysfunction. Examples of both lymphocytic infiltration of organs (eg, lymphocytic interstitial pneumonitis) and autoantibody production



▲ Figure 31-1. Relationship of CD4 count to development of opportunistic infections. MAC, *Mycobacterium avium* complex; CMV, cytomegalovirus; CNS, central nervous system.

(eg, immunologic thrombocytopenia) occur. These phenomena may be the only clinically apparent disease or may coexist with obvious immunodeficiency. Moreover, HIV-infected individuals appear to have higher rates of allergic reactions to unknown allergens as seen with eosinophilic pustular folliculitis (“itchy red bump syndrome”) as well as increased rates of hypersensitivity reactions to medications (for example, the fever and sunburn-like rash seen with trimethoprim-sulfamethoxazole reactions).

Clinical Findings

The complications of HIV-related infections and neoplasms affect virtually every organ. The general approach to the HIV-infected person with symptoms is to evaluate the organ systems involved, aiming to diagnose treatable conditions rapidly. As can be seen in Figure 31-1, the CD4 lymphocyte count result enables the clinician to focus on the diagnoses most likely to be seen at each stage of immunodeficiency. Certain infections may occur at any CD4 count, while others rarely occur unless the CD4 lymphocyte count has dropped below a certain level. For example, a patient with a CD4 count of 600 cells/mcL, cough, and fever may have a bacterial pneumonia but would be very unlikely to have *Pneumocystis* pneumonia.

A. Symptoms and Signs

Many individuals with HIV infection remain asymptomatic for years even without antiretroviral treatment, with a mean time of approximately 10 years between infection

and development of AIDS. When symptoms occur, they may be remarkably protean and nonspecific. Since virtually all the findings may be seen with other diseases, a combination of complaints is more suggestive of HIV infection than any one symptom.

Physical examination may be entirely normal. Abnormal findings range from completely nonspecific to highly specific for HIV infection. Those that are specific for HIV infection include hairy leukoplakia of the tongue, disseminated Kaposi sarcoma, and cutaneous bacillary angiomatosis. Generalized lymphadenopathy is common early in infection.

The specific presentations and management of the various complications of HIV infection are discussed under the Complications section below.

- Brew BJ et al. Neurologic sequelae of primary HIV infection. *Handb Clin Neurol.* 2018;152:65. [PMID: 29604985]
- Chen B. Molecular mechanism of HIV-1 entry. *Trends Microbiol.* 2019;27:878. [PMID: 31262533]
- Fida M et al. Dolutegravir plus lamivudine dual therapy—a new option for initial antiretroviral therapy. *Drugs Today (Barc).* 2019;55:297. [PMID: 31131840]
- Tavassoli S et al. Peripheral ulcerative keratitis with corneal melt as the primary presentation in a case of human immunodeficiency virus. *BMJ Case Rep.* 2019;12:e226936. [PMID: 30798272]

B. Laboratory Findings

Specific tests for HIV include antibody, antigen, and viral load detection (Table 31-2). Initial testing for HIV should

Table 31–2. Commonly ordered tests for HIV infection.

Test	Significance
HIV-1/2 antigen/antibody immunoassay	Detects antibodies for HIV-1 and HIV-2 along with HIV-1 p24 antigen. Positive specimens require testing with HIV-1/HIV-2 antibody differentiation assay.
HIV-1/HIV-2 antibody differentiation immunoassay	Serves as confirmatory test and differentiates HIV-1 and HIV-2. Tests that are reactive on HIV-1/2 antigen/antibody immunoassay but negative on this confirmatory test should have a HIV-1 viral load test. Sensitivity and specificity of combination of reactive antigen/antibody immunoassay and positive differentiation assay approach 100% for chronic infection.
HIV rapid antibody test	Screening test for HIV. Produces results in 10–20 minutes. Can be performed by personnel with limited training. Sensitivity and specificity for chronic infection are > 99%. Positive results must be confirmed with standard HIV testing using the HIV-1/2 antigen/antibody immunoassay and the HIV-1/HIV-2 antibody differentiation assay.
HIV-1 viral load tests	This nucleic acid test measures the amount of actively replicating HIV virus. Patients who are negative on the HIV-1/2 antigen/antibody immunoassay and/or the HIV-1/HIV-2 antibody differentiation assay but have a positive HIV viral load are likely experiencing acute HIV infection; however, caution is warranted when the test result shows low-level viremia (ie, < 1000 copies/mL) as this may represent a false-positive result. Besides its use in diagnosing acute HIV infection, HIV viral load is the most accurate indicator of viral activity and response to treatment.
Absolute CD4 lymphocyte count	Best test for determining stage of HIV infection. Risk of progression to an AIDS opportunistic infection or malignancy is high with CD4 count is < 200 cells/mcL in the absence of treatment.
CD4 lymphocyte percentage	Percentage may be more reliable than the CD4 count. Risk of progression to an AIDS opportunistic infection or malignancy is high with percentage < 14% in the absence of treatment.

be done using a fourth-generation HIV antigen/antibody immunoassay. It detects HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen. Reactive specimens are then tested with an HIV-1/HIV-2 differentiation immunoassay to confirm infection and to distinguish HIV-1 from HIV-2. For patients who are reactive on both tests, the sensitivity and specificity for chronic HIV approaches 100%. Patients who have a reactive HIV antigen/antibody immunoassay but a negative HIV-1/HIV-2 differentiation immunoassay should have a HIV-1 viral load test (nucleic acid test); those with positive viral loads despite negative antibodies are likely having acute HIV infection. Persons who are reactive on the initial test and then negative on the confirmatory test and have nondetectable viral loads are presumed to have a false-positive test, which may occur with recent influenza vaccination, autoantibodies (eg, with collagen vascular or autoimmune diseases), or alloantibodies from pregnancy. With fourth-generation tests, antibodies will be detectable in 95% of persons within 6 weeks after infection.

Rapid HIV antibody tests of blood or oral fluid provide results within 10–20 minutes and can be performed in clinician offices, including by personnel without laboratory training and without a Clinical Laboratory Improvement Amendment (CLIA)-approved laboratory. Persons who test positive on a rapid test require confirmation with a standard testing as above. Rapid testing is particularly helpful in settings where a result is needed immediately (eg, a woman in labor who has not recently been tested for HIV) or when the patient is unlikely to return for a result. Rapid HIV home tests that allow the testers to learn their status privately by simply swabbing along their gum lines are also available (www.oraquick.com).

Nonspecific laboratory findings with HIV infection may include anemia, leukopenia (particularly lymphopenia), and thrombocytopenia in any combination, elevation of the erythrocyte sedimentation rate, polyclonal hypergammaglobulinemia, and hypcholesterolemia. Cutaneous anergy is common with immunosuppression.

The absolute CD4 lymphocyte count is the most widely used marker to provide prognostic information and to guide therapy decisions (Table 31–2). As counts decrease, the risk of serious opportunistic infection over the subsequent 3–5 years increases. There are many limitations to using the CD4 count, including diurnal variation, depression with intercurrent illness, and intra-laboratory and interlaboratory variability. Therefore, the trend is more important than a single determination. The frequency of performance of counts depends on the patient's health status and whether or not they are receiving antiretroviral treatment. All patients regardless of CD4 count should be offered antiretroviral treatment; CD4 counts should be monitored every 3–6 months in patients taking antiretroviral treatment consistently. Initiation of *Pneumocystis jirovecii* prophylactic therapy is recommended when the CD4 count drops below 200 cells/mcL, and initiation of *Mycobacterium avium* prophylaxis is recommended when the CD4 count drops below 75–100 cells/mcL. Some studies suggest that the percentage of CD4 lymphocytes is a more reliable indicator of prognosis than the absolute counts because the percentage does not depend on calculating a manual differential. While the CD4 count measures immune dysfunction, it does not provide a measure of how actively HIV is replicating in the body. **HIV viral load** tests assess the level of viral replication and provide useful

prognostic information that is independent of the information provided by CD4 counts.

Differential Diagnosis

HIV infection may mimic a variety of other medical illnesses. Specific differential diagnosis depends on the mode of presentation. In patients presenting with constitutional symptoms such as weight loss and fevers, differential considerations include cancer, chronic infections such as tuberculosis and endocarditis, and endocrinologic diseases such as hyperthyroidism. When pulmonary processes dominate the presentation, acute and chronic lung infections must be considered as well as other causes of diffuse interstitial pulmonary infiltrates, including SARS-CoV-2 infection (COVID-19). When neurologic disease is the mode of presentation, conditions that cause mental status changes or neuropathy—eg, alcohol use disorder (alcoholism), liver disease, kidney dysfunction, thyroid disease, and vitamin deficiency—should be considered. If a patient presents with headache and a cerebrospinal fluid pleocytosis, other causes of chronic meningitis enter the differential. When diarrhea is a prominent complaint, infectious enterocolitis, antibiotic-associated colitis, inflammatory bowel disease, and malabsorptive syndromes must be considered.

Complications

A. Systemic Complaints

Fever, night sweats, and weight loss are common symptoms in HIV-infected patients and may occur without a complicating opportunistic infection. Patients with persistent fever and no localizing symptoms should nonetheless be carefully examined, and evaluated with a chest radiograph (*Pneumocystis* pneumonia can present without respiratory symptoms), bacterial blood cultures if the fever is greater than 38.5°C, serum cryptococcal antigen, and mycobacterial cultures of the blood. Sinus CT scans should be considered to evaluate occult sinusitis. If these studies are normal, patients should be observed closely. Antipyretics are useful to prevent dehydration.

Centers for Disease Control and Prevention. 2018 quick reference guide: Recommended laboratory HIV testing algorithm for serum or plasma specimens. <https://stacks.cdc.gov/view/cdc/50872>

Erlandson KM et al. HIV and aging: reconsidering the approach to management of comorbidities. *Infect Dis Clin North Am.* 2019;33:769. [PMID: 31395144]

Pahwa S et al. NIH Workshop on HIV-associated comorbidities, coinfections, and complications: summary and recommendation for future research. *J Acquir Immune Defic Syndr.* 2021; 86:11. [PMID: 33306561]

A. PRESENTATION—AIDS patients frequently suffer from anorexia, nausea, and vomiting, all of which contribute to weight loss by decreasing caloric intake. In some cases, these symptoms are secondary to a specific infection, such as viral hepatitis. In other cases, however, evaluation of the symptoms yields no specific pathogen, and it is assumed to be due to a primary effect of HIV. Malabsorption also plays a role in decreased caloric intake. Patients may suffer diarrhea from infections with bacterial, viral, or parasitic agents.

Exacerbating the decrease in caloric intake, many AIDS patients have an increased metabolic rate. This increased rate has been shown to exist even among asymptomatic HIV-infected persons, but it accelerates with disease progression and secondary infection. AIDS patients with secondary infections also have decreased protein synthesis, which makes maintaining muscle mass difficult.

B. MANAGEMENT—Several strategies have been developed to slow AIDS wasting. In the long term, nothing is as effective as antiretroviral treatment, since it treats the underlying HIV infection. In the short term, effective fever control decreases the metabolic rate and may slow the pace of weight loss, as does treating any underlying opportunistic infection. Food supplementation with high-calorie drinks may enable patients with not much appetite to maintain their intake. Selected patients with otherwise good functional status and weight loss due to unrelenting nausea, vomiting, or diarrhea may benefit from total parenteral nutrition (TPN). It should be noted, however, that TPN is more likely to increase fat stores than to reverse the muscle wasting process.

Two pharmacologic approaches for increasing appetite and weight gain are the progestational agent **megestrol acetate** liquid suspension (400–800 mg orally daily in divided doses) and the antiemetic agent **dronabinol** (2.5–5 mg orally three times a day), but neither of these agents increases lean body mass. Side effects from megestrol acetate are rare, but thromboembolic phenomena, edema, nausea, vomiting, and rash have been reported. In 3–10% of patients using dronabinol, euphoria, dizziness, paranoia, and somnolence and even nausea and vomiting have been reported. Dronabinol contains only one of the active ingredients in marijuana, and many patients report better relief of nausea and improvement of appetite with **medical cannabis** (administered via smoking, vaporization, essential oils, or cooked in food). In the United States, 34 states and the District of Columbia have legalized medical marijuana, and 13 states have legalized recreational (non-medical) use. However, the use and sale of marijuana are still illegal under federal law.

Two regimens that have resulted in increases in lean body mass are growth hormone and anabolic steroids. **Growth hormone** at a dose of 0.1 mg/kg/day (up to 6 mg) subcutaneously for 12 weeks has resulted in modest increases in lean body mass. Treatment with growth hormone can cost as much as \$10,000 per month. **Anabolic steroids** also increase lean body mass among HIV-infected patients. They seem to work best for patients who are able to do weight training. The most commonly used regimens are testosterone enanthate or testosterone cypionate (100–200 mg intramuscularly every 2–4 weeks).

1. Weight loss and wasting syndrome—Weight loss is a particularly distressing complication of long-standing HIV infection. Patients typically have disproportionate loss of muscle mass, with maintenance or less substantial loss of fat stores. The mechanism of HIV-related weight loss is not completely understood but appears to be multifactorial.

Testosterone transdermal system (apply 5 mg system each evening) and testosterone gel (1%; apply a 5-g packet [50 mg testosterone] to clean, dry skin daily) are also available. The anabolic steroid oxandrolone (20 mg orally in two divided doses) has also been found to increase lean body mass.

Badowski ME et al. Dronabinol oral solution in the management of anorexia and weight loss in AIDS and cancer. *Ther Clin Risk Manag.* 2018;14:643. [PMID: 29670357]

Harrison ME et al. Use of cyproheptadine to stimulate appetite and body weight gain: a systematic review. *Appetite.* 2019;137: 62. [PMID: 30825493]

2. Nausea—Nausea leading to weight loss is sometimes due to esophageal candidiasis. Patients with oral candidiasis and nausea should be empirically treated with an oral antifungal agent. Patients with weight loss due to nausea of unclear origin may benefit from use of antiemetics prior to meals (prochlorperazine, 10 mg three times daily; metoclopramide, 10 mg three times daily; or ondansetron, 8 mg three times daily). Dronabinol (5 mg three times daily) or medical cannabis can also be used to treat nausea. Depression and adrenal insufficiency are two potentially treatable causes of weight loss.

Hall VP. Common gastrointestinal complications associated with human immunodeficiency virus/AIDS: an overview. *Crit Care Nurs Clin North Am.* 2018;30:101. [PMID: 29413205]

Unal E et al. Cannabinoids: a guide for use in the world of gastrointestinal disease. *J Clin Gastroenterol.* 2020;54:769. [PMID: 31789770]

B. Pulmonary Disease

1. *Pneumocystis* pneumonia—(See also Chapter 36.) *P. jirovecii* pneumonia is the most common opportunistic infection associated with AIDS. *Pneumocystis* pneumonia may be difficult to diagnose because the symptoms—fever, cough, and shortness of breath—are nonspecific. Furthermore, the severity of symptoms ranges from fever and no respiratory symptoms through mild cough or dyspnea to frank respiratory distress.

Hypoxemia may be severe, with a Po_2 less than 60 mm Hg. The cornerstone of diagnosis is the chest radiograph (Figure 31–2). Diffuse or perihilar infiltrates are most characteristic, but only two-thirds of patients with *Pneumocystis* pneumonia have this finding. Normal chest radiographs are seen in 5–10% of patients with *Pneumocystis* pneumonia, while the remainder have atypical infiltrates. Apical infiltrates are commonly seen among patients with *Pneumocystis* pneumonia who have been receiving aerosolized pentamidine prophylaxis. Large pleural effusions are uncommon with *Pneumocystis* pneumonia; their presence suggests bacterial pneumonia, other infections such as tuberculosis, or pleural Kaposi sarcoma.

Definitive diagnosis can be obtained in 50–80% of cases by Wright-Giemsa stain or direct fluorescence antibody (DFA) test of induced sputum. Sputum induction is performed by having patients inhale an aerosolized solution of 3% saline produced by an ultrasonic nebulizer. Patients should not eat for at least 8 hours and should not use



▲ **Figure 31–2.** *Pneumocystis* pneumonia in a Haitian woman suspected of having underlying HIV/AIDS. Typical chest radiograph showing bilateral diffuse interstitial infiltrates extending out from the hilar areas. (Reproduced, with permission, from Grippi MA, Elias JA, Fishman JA et al (editors). *Fishman's Pulmonary Diseases and Disorders*, 5th ed. McGraw-Hill, 2015.)

toothpaste or mouthwash prior to the procedure since they can interfere with test interpretation. The next step for patients with negative sputum examinations in whom *Pneumocystis* pneumonia is still suspected should be bronchoalveolar lavage. This technique establishes the diagnosis in over 95% of cases.

In patients with symptoms suggestive of *Pneumocystis* pneumonia but with negative or atypical chest radiographs and negative sputum examinations, other diagnostic tests may provide additional information in deciding whether to proceed to bronchoalveolar lavage. Elevation of serum lactate dehydrogenase occurs in 95% of cases of *Pneumocystis* pneumonia, but the specificity of this finding is at best 75%. A serum beta-glucan test is a more sensitive and specific test for *Pneumocystis* pneumonia compared with serum lactate dehydrogenase and may avoid more invasive tests when used in the appropriate clinical setting. Either a normal diffusing capacity of carbon monoxide (DL_{CO}) or a high-resolution CT scan of the chest that demonstrates no interstitial lung disease makes the diagnosis of *Pneumocystis* pneumonia very unlikely. In addition, a CD4 count greater than 250 cells/mcL within 2 months prior to evaluation of respiratory symptoms makes a diagnosis of *Pneumocystis* pneumonia unlikely; only 1–5% of cases occur above this CD4 count level (Figure 31–1). This is true even if the patient previously had a CD4 count lower than 200 cells/mcL but has had an increase with antiretroviral treatment. Pneumothoraces can be seen in HIV-infected patients with a history of *Pneumocystis* pneumonia.

Trimethoprim-sulfamethoxazole is the preferred treatment of *Pneumocystis* pneumonia (Table 31–3). In addition to specific anti-*Pneumocystis* treatment, corticosteroid therapy has been shown to improve the course of patients

Table 31–3. Treatment of AIDS-related opportunistic infections and malignancies.¹

Infection or Malignancy	Treatment	Complications ²
<i>Pneumocystis jirovecii</i> infection ³	Preferred regimen: Trimethoprim-sulfamethoxazole, 15 mg/kg/day (based on trimethoprim component) intravenously or one double-strength tablet orally three times a day for 21 days. Add prednisone when $\text{PaO}_2 < 70 \text{ mm Hg}$ on room air or alveolar-arterial O_2 gradient $> 35 \text{ mm Hg}$: 40 mg orally twice a day on days 1–5, 40 mg orally daily on days 6–10, 20 mg orally daily on days 11–21	Nausea, neutropenia, anemia, hepatitis, rash, Stevens-Johnson syndrome
	Pentamidine, 3–4 mg/kg/day intravenously for 21 days plus prednisone when indicated as above	Hypotension, hypoglycemia, anemia, neutropenia, pancreatitis, hepatitis
	Primaquine, 30 mg/day orally, and clindamycin, 600 mg every 8 hours orally, for 21 days plus prednisone when indicated as above	Primaquine: hemolytic anemia in G6PD-deficient patients, ³ methemoglobinemia, neutropenia, colitis Clindamycin: rash, nausea, abdominal pain, colitis
	Not recommended for severe disease: Trimethoprim, 15 mg/kg/day orally in three divided doses, with dapsone, 100 mg/day orally, for 21 days, ³ plus prednisone when indicated as above	Nausea, rash, hemolytic anemia in G6PD-deficient patients; methemoglobinemia (weekly levels should be $< 10\%$ of total hemoglobin)
	Not recommended for severe disease: Atovaquone, 750 mg orally twice daily with food for 21 days, plus prednisone when indicated as above	Rash, elevated aminotransferases, anemia, neutropenia
<i>Mycobacterium avium</i> complex infection	Clarithromycin, 500 mg orally twice daily with ethambutol, 15 mg/kg/day orally (maximum, 1 g). May also add: Rifabutin, 300 mg orally daily	Clarithromycin: hepatitis, nausea, diarrhea Ethambutol: hepatitis, optic neuritis Rash, hepatitis, uveitis
Toxoplasmosis	Preferred regimen: Pyrimethamine, 200 mg orally as loading dose, followed by 50 mg daily (weight $\leq 60 \text{ kg}$) or 75 mg daily (weight $> 60 \text{ kg}$), combined with sulfadiazine, 1000 mg orally four times daily (weight $\leq 60 \text{ kg}$) or 1500 mg orally four times daily (weight $> 60 \text{ kg}$) and leucovorin 10–25 mg orally daily for at least 6 weeks. Longer courses are necessary for extensive disease or incomplete clinical or radiographic resolution. Maintenance therapy with pyrimethamine 25–50 mg orally plus sulfadiazine 2000–4000 mg in two to four divided doses plus leucovorin 10–25 mg orally daily. Long-term treatment should be maintained until immune reconstitution with antiretroviral treatment occurs.	Pyrimethamine: leukopenia, anorexia, vomiting Sulfadiazine: nausea, vomiting, Stevens-Johnson syndrome
	For patients who are intolerant of sulfa who cannot be desensitized: Substitute clindamycin 600 mg intravenously or orally every 6 hours for the sulfadiazine in the above regimen	Pyrimethamine: leukopenia, anorexia, vomiting Clindamycin: rash, nausea, abdominal pain, colitis
	If pyrimethamine not available: Trimethoprim-sulfamethoxazole, 10 mg/kg/day (based on trimethoprim component)	Nausea, neutropenia, anemia, hepatitis, rash, Stevens-Johnson syndrome
Non-Hodgkin lymphoma	Combination chemotherapy (eg, EPOCH with rituximab and G-CSF). Central nervous system disease: Radiation treatment with dexamethasone for edema	Nausea, vomiting, anemia, neutropenia, thrombocytopenia, cardiac toxicity (with doxorubicin)
Cryptococcal meningitis	Preferred regimen: Induction: Liposomal amphotericin B, 3–4 mg/kg/day intravenously, with flucytosine, 25 mg/kg/dose orally four times daily for minimum of 2 weeks (adjust flucytosine dose for kidney function), then fluconazole, 400 mg orally daily for a minimum of 8 weeks (consolidation), then 200 mg orally daily to complete a minimum of 1 year of therapy (maintenance)	Liposomal amphotericin: fever, chills, hypokalemia, kidney disease Flucytosine: bone marrow suppression, kidney disease, hepatitis Fluconazole: hepatitis
	Induction: Amphotericin B, 0.7–1.0 mg/kg/day intravenously, with flucytosine, 25 mg/kg/dose orally four times daily for a minimum of 2 weeks (adjust flucytosine dose for kidney function), then fluconazole, 400 mg orally daily for a minimum of 8 weeks (consolidation), then 200 mg orally daily to complete a minimum of 1 year of therapy (maintenance)	Amphotericin: fever, chills, hypokalemia, kidney disease Flucytosine: bone marrow suppression, kidney disease, hepatitis Fluconazole: hepatitis

(continued)

Table 31–3. Treatment of AIDS-related opportunistic infections and malignancies.¹ (continued)

Infection or Malignancy	Treatment	Complications ²
Cryptococcal meningitis (cont.)	Fluconazole, used alone, is inferior to amphotericin B as induction therapy; it is recommended only for patients who cannot tolerate or do not respond to the preferred regimen above. If used for primary induction therapy, give fluconazole, 1200 mg orally daily, with flucytosine, 25 mg/kg/dose orally four times daily for a minimum of 2 weeks (adjust flucytosine dose for kidney function), then 400 mg orally daily for a minimum of 8 weeks (consolidation), then 200 mg orally daily to complete a minimum of 1 year of therapy.	Hepatitis
Cytomegalovirus retinitis (immediate sight-threatening)	Preferred regimen: First-line therapy is oral valganciclovir, 900 mg orally twice a day with food for 21 days followed by 900 mg daily (maintenance). For sight-threatening infections involving the macula or optic nerve, add intravitreal ganciclovir (2 mg/injection) or foscarnet (2.4 mg/injection) for 1–4 doses/day for 7–10 days Ganciclovir, 10 mg/kg/day intravenously in two divided doses for 14–21 days, followed by 5 mg/kg daily (maintenance) Foscarnet, 90 mg/kg intravenously every 12 hours for 14 days, followed by 90–120 mg/kg once daily Cidofovir, 5 mg/kg/week intravenously for 2 weeks, then 5 mg/kg every other week with probenecid, 2 g orally 3 hours before dose, 1 g orally 2 hours after dose, and 1 g orally 8 hours after dose	For valganciclovir: Neutropenia, anemia, thrombocytopenia (avoid in patients with hemoglobin < 8 g/dL, neutrophil count below 500 cells/mcL [0.5 × 10 ⁹ /L] or platelet count below 25,000/mcL [25 × 10 ⁹ /L]). Potentially embryotoxic. Neutropenia, anemia, thrombocytopenia Adjust ganciclovir dose for kidney function. Potentially embryotoxic. Nausea, hypokalemia, hypocalcemia, hyperphosphatemia, azotemia Adjust foscarnet dose for kidney function. Nephrotoxicity (to reduce likelihood, pre- and post-saline hydration, along with probenecid), ocular hypotony, anterior uveitis, neutropenia Avoid in patients with sulfa allergy because of cross hypersensitivity with probenecid
Esophageal candidiasis or recurrent vaginal candidiasis	Fluconazole, 100–200 mg orally daily for 14–21 days for esophageal disease and > 7 days for recurrent vaginal disease	Hepatitis, development of azole resistance. Fluconazole should not be given to women who are or may be pregnant because of risk of spontaneous abortion.
Herpes simplex infection	Acyclovir, 400 mg orally three times daily for 5–10 days; or acyclovir, 5 mg/kg intravenously every 8 hours for severe cases Famciclovir, 500 mg orally twice daily for 5–10 days Valacyclovir, 1 g orally twice daily for 5–10 days Foscarnet, 40 mg/kg intravenously every 8 hours, for acyclovir-resistant cases	Resistant herpes simplex with long-term therapy Nausea Nausea Nausea, hypokalemia, hypocalcemia, hyperphosphatemia, azotemia Adjust foscarnet dose for kidney function
Herpes zoster	Preferred regimen: Valacyclovir, 1000 mg orally three times daily for 7–10 days Preferred regimen: Famciclovir, 500 mg orally three times daily for 7–10 days Acyclovir, 800 mg orally five times daily for 7–10 days. Intravenous therapy at 10 mg/kg every 8 hours for extensive cutaneous or visceral disease until clinical improvement, then switch to oral therapy to complete a 10- to 14-day course. For ocular involvement, consult an ophthalmologist immediately.	Nausea Nausea Nausea
Kaposi sarcoma	Initiation or optimization of antiretroviral treatment Combination chemotherapy (eg, daunorubicin, bleomycin, vinblastine) Pomalidomide, 5 mg/day orally on days 1–21 of every 28-day cycle; alternative to chemotherapy	Side effects of antiretroviral treatment Bone marrow suppression, cardiac toxicity (with daunorubicin), fever Fatigue, asthenia, dyspnea, anemia, neutropenia; contraindicated in pregnancy

¹Recommendations drawn from Centers for Disease Control and Prevention. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. February 11, 2020. Downloaded from <https://aidsinfo.nih.gov/guidelines> on February 14, 2020.

²List of complications is not exhaustive.

³Prior to use of primaquine or dapsone, check glucose-6-phosphate dehydrogenase (G6PD) level in Black patients and those of Mediterranean origin.

EPOCH, etoposide, prednisolone, vincristine (Oncovin), cyclophosphamide, doxorubicin (hydroxydaunomycin); G-CSF, granulocyte colony-stimulating factor (filgrastim).

with moderate to severe *P jirovecii* pneumonia (Pao_2 less than 70 mm Hg on room air or alveolar-arterial O_2 gradient greater or equal to 35 mm Hg) when administered within 72 hours of the start of anti-*Pneumocystis* treatment. It should be started as early as possible after initiation of treatment, using prednisone 40 mg orally twice daily for days 1–5, 40 mg daily for days 6–10, and 20 mg daily for days 11–21 (for patients who cannot take oral medication, intravenous methylprednisolone can be substituted at 75% of the oral dose). The mechanism of action is presumed to be a decrease in alveolar inflammation.

Fishman JA. *Pneumocystis jirovecii*. Semin Respir Crit Care Med. 2020;41:141. [PMID: 32000290]

Shibata S et al. Pneumocystis pneumonia in HIV-1-infected patients. Respir Investig. 2019;57:213. [PMID: 30824356]

Tasaka S. Recent advances in the diagnosis and management of *Pneumocystis* pneumonia. Tuberc Respir Dis (Seoul). 2020;83:132. [PMID: 32185915]

US Department of Health and Human Services. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV. 2020. <https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/whats-new-guidelines>

2. Other infectious pulmonary diseases—Other infectious causes of pulmonary disease in AIDS patients include bacterial, mycobacterial, and viral etiologies.

A. BACTERIAL—Community-acquired pneumonia is the most common cause of pulmonary disease in HIV-infected persons. An increased incidence of pneumococcal pneumonia with septicemia and *Haemophilus influenzae* pneumonia has been reported. *Pseudomonas aeruginosa* is an important respiratory pathogen in advanced disease and, more rarely, pneumonia from *Rhodococcus equi* infection can occur.

B. MYCOBACTERIAL—The incidence of infection with *Mycobacterium tuberculosis* has markedly increased in metropolitan areas because of HIV infection as well as homelessness. Tuberculosis occurs in an estimated 4% of persons in the United States who have AIDS. Patients with active tuberculosis and CD4 counts above 350 cells/mcL are likely to present with upper lobe and hilar infiltrates and paratracheal adenopathy, findings similar to persons uninfected with HIV (Figure 31–3). With advanced immunodeficiency, lower lobe, middle lobe, interstitial, and miliary infiltrates are more common, along with mediastinal adenopathy and extrapulmonary involvement. Although a purified protein derivative (PPD) test or an **interferon gamma release assay (IGRA)**, including the QuantiFERON and T-SPOT tests) should be performed on all HIV-infected persons in whom a diagnosis of tuberculosis is being considered, the lower the CD4 cell count, the greater the likelihood of falsely negative PPD or IGRA test results or of indeterminate IGRA test results.

Treatment of HIV-infected persons with active tuberculosis is similar to treatment of HIV-uninfected tubercular individuals. However, rifampin should not be given to patients receiving a boosted protease inhibitor (PI) regimen. In these cases, rifabutin may be substituted, but it may require dosing modifications depending on the



▲ Figure 31–3. A 36-year-old man with **pulmonary tuberculosis**. There is an opacification of a portion of the left upper lung in association with a cavity, findings consistent with pulmonary tuberculosis. Also, there is an infiltrate in the right lung. The extent of his disease raises the specter that he has underlying HIV/AIDS.

(Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

antiretroviral regimen. Multidrug-resistant tuberculosis has been a major problem in several metropolitan areas of the developed world, and reports from South Africa of “extremely resistant” tuberculosis in AIDS patients are a growing global concern. Noncompliance with prescribed antituberculous medications is a major risk factor. Several of the reported outbreaks appear to implicate nosocomial spread. The emergence of medication resistance makes it essential that antibiotic sensitivities be performed on all positive cultures. Medication therapy should be individualized. Patients with multidrug-resistant *M tuberculosis* infection should receive at least three medications to which their organism is sensitive.

Atypical mycobacteria can cause pulmonary disease in AIDS patients with or without preexisting lung disease and responds variably to treatment. Distinguishing between *M tuberculosis* and atypical mycobacteria requires culture of sputum specimens. DNA probes allow for presumptive identification usually within days of a positive culture. While awaiting definitive diagnosis, clinicians should err on the side of treating patients as if they have *M tuberculosis* infection unless the risk of atypical mycobacteria is very high (eg, a person without risk for tuberculosis exposure with a CD4 count under 50 cells/mcL—see Figure 31–1), clinicians may wait for definitive diagnosis, and the person is smear-negative for acid-fast bacilli, clinically stable, and not living in a communal setting.

Blanc FX et al; STATIS ANRS 12290 Trial Team. Systematic or test-guided treatment for tuberculosis in HIV-infected adults. N Engl J Med. 2020;382:2397. [PMID: 32558469]

- Kerkhoff AD et al. Virtual CROI 2020: Tuberculosis and coinfections in HIV infection. *Top Antivir Med.* 2020;28:455. [PMID: 32886465]
- Lapinel NC et al. Prevalence of non-tuberculous mycobacteria in HIV-infected patients admitted to hospital with pneumonia. *Int J Tuberc Lung Dis.* 2019;23:491. [PMID: 31064629]

C. VIRAL (SARS-CoV-2 AND OTHER)—COVID-19, the illness caused by the novel 2019 coronavirus SARS-CoV-2, causes a very wide spectrum of illness, ranging from no symptoms, to a mild upper respiratory tract illness with fever and cough, to a clinical triad of fever, cough, and dyspnea, to pneumonia, to acute respiratory distress syndrome (ARDS), and even to fulminant multisystem organ failure and death. Chest radiographs and CT scans may be normal early in the disease course, then may show nonspecific diffuse ground glass opacities, multilobar infiltrates, and consolidations, some progressing to full-blown ARDS (see Chapter 32).

The limited data currently available do not indicate that the disease course of COVID-19 in persons with HIV differs from that in persons without HIV. Those patients with HIV who have other comorbidities (eg, cardiovascular disease, lung disease, long-term smoking) have an increased risk of a more severe course of COVID-19 illness.

Persons with HIV should not alter their antiretroviral regimens or add medications for the purpose of possibly preventing or treating SARS-CoV-2 infection. Patients who have a suppressed HIV viral load and are in stable health should postpone routine medical and laboratory visits if possible, and clinicians should use telephone or virtual visits to replace face-to-face encounters for nonurgent care and adherence counseling. CDC guidelines advise patients with HIV to maintain on-hand at least a 30-day—and ideally a 90-day—supply of antiretroviral drugs and other medications, and to change to pharmacy or mail order delivery of medications when possible. Persons with HIV may need additional assistance with food, housing, transportation, and childcare.

For persons with HIV in self-isolation or quarantine due to SARS-CoV-2 exposure, clinicians should devise a plan to evaluate patients if they develop COVID-19-related persistent fever, cough, or dyspnea, including possible transfer to a health care facility for care. When a person with HIV is hospitalized for presumed COVID-19, antiretroviral therapy should be continued. If the patient's medications are not on the hospital's formulary, the clinician may need to write an order that medications from the patients' home supplies can be administered. Antiretroviral drug substitutions should be avoided.

Although information and data are rapidly evolving, it seems that persons with HIV on a suppressive antiretroviral regimen who contract COVID-19 have a prognosis similar to, and can be managed clinically the same as, persons who do not have HIV. However, additional caution is warranted for HIV-infected persons who develop COVID-19, especially those with poorly controlled HIV or advanced AIDS.

Isolation of cytomegalovirus (CMV) from bronchoalveolar lavage fluid occurs commonly in AIDS patients but does not establish a definitive diagnosis. Diagnosis of CMV

pneumonia requires biopsy; response to treatment is poor. Histoplasmosis, coccidioidomycosis, and cryptococcal disease as well as more common respiratory viral infections should also be considered in the differential diagnosis of unexplained pulmonary infiltrates.

Centers for Disease Control and Prevention. What to know about HIV and COVID-19. Updated 2021 Feb 1. <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/hiv.html>

Guo W et al. Patterns of HIV and SARS-CoV-2 co-infection in Wuhan, China. *J Int AIDS Soc.* 2020;23:e25568. [PMID: 32697865]

US Department of Health and Human Services. Interim guidance for COVID-19 and persons with HIV. <https://clinicalinfo.hiv.gov/en/guidelines/covid-19-and-persons-hiv-interim-guidance/interim-guidance-covid-19-and-persons-hiv>. Updated 2021 Feb 26.

Vizcarra P et al; COVID-19 ID Team. Description of COVID-19 in HIV-infected individuals: a single-centre, prospective cohort. *Lancet HIV.* 2020;7:e554. [PMID: 32473657]

3. Noninfectious pulmonary diseases—

A. PRESENTATION—Noninfectious causes of lung disease include Kaposi sarcoma, non-Hodgkin lymphoma, interstitial pneumonitis, and increasingly, in the current antiretroviral treatment era, lung cancer. In patients with known Kaposi sarcoma, pulmonary involvement complicates the course in approximately one-third of cases. However, pulmonary involvement is rarely the presenting manifestation of Kaposi sarcoma. Non-Hodgkin lymphoma may involve the lung as the sole site of disease, but more commonly involves other organs as well, especially the brain, liver, and gastrointestinal tract. Both of these processes may show nodular or diffuse parenchymal involvement, pleural effusions, and mediastinal adenopathy on chest radiographs.

Nonspecific interstitial pneumonitis may mimic *Pneumocystis* pneumonia. Lymphocytic interstitial pneumonitis seen in lung biopsies has a variable clinical course. Typically, these patients present with several months of mild cough and dyspnea; chest radiographs show interstitial infiltrates. Many patients with this entity undergo transbronchial biopsies in an attempt to diagnose *Pneumocystis* pneumonia. Instead, the tissue shows interstitial inflammation ranging from an intense lymphocytic infiltration (consistent with lymphoid interstitial pneumonitis) to a mild mononuclear inflammation.

B. MANAGEMENT—Corticosteroids may be helpful in some cases refractory to antiretroviral treatment.

Maitre T et al. Increasing burden of noninfectious lung disease in persons living with HIV: a 7-year study using the French nationwide hospital administrative database. *Eur Respir J.* 2018;52:1800359. [PMID: 30139778]

4. Sinusitis—

A. PRESENTATION—Chronic sinusitis can be a frustrating problem for HIV-infected patients. Symptoms include sinus congestion and discharge, headache, and fever. Some patients may have radiographic evidence of sinus disease on sinus CT scan in the absence of significant symptoms.

B. MANAGEMENT—HIV-infected patients with purulent drainage should be treated for possible *H influenzae* with amoxicillin-potassium clavulanate (500 mg orally three times a day) (see Chapter 8). A 7-day course of pseudoephedrine 60 mg twice daily may be helpful in decreasing congestion. Prolonged treatment (3–6 weeks) with an antibiotic and guaifenesin (600 mg orally twice daily) is sometimes necessary. For patients not responding to amoxicillin-potassium clavulanate, levofloxacin may be tried (400 mg orally daily). In patients with advanced immunodeficiency, *Pseudomonas* infections should be suspected, especially if there is not a response to first-line antibiotics. Some patients may require referral to an otolaryngologist for sinus drainage and culture for possible fungal infection (*Aspergillus*, *Histoplasma capsulatum*).

Bao S et al. Otorhinolaryngological profile and surgical intervention in patients with HIV/AIDS. *Sci Rep.* 2018;8:12045. [PMID: 30104657]

Nabet C et al. *Histoplasma capsulatum* causing sinusitis: a case report in French Guiana and review of the literature. *BMC Infect Dis.* 2018;18:595. [PMID: 30477434]

C. Central Nervous System Disease

Central nervous system disease in HIV-infected patients can be divided into intracerebral space-occupying lesions, encephalopathy, meningitis, and spinal cord processes. Many of these complications have declined markedly in prevalence in the era of effective antiretroviral treatment. Cognitive declines, however, may be more common in HIV patients, especially as they age (older than 50 years), even those who are taking fully suppressive antiretroviral treatment.

Stephens RJ et al. Central nervous system infections in the immunocompromised adult presenting to the emergency department. *Emerg Med Clin North Am.* 2021;39:101. [PMID: 33218652]

1. Toxoplasmosis—Toxoplasmosis is the most common CNS space-occupying lesion in HIV-infected patients. Headache, focal neurologic deficits, seizures, or altered mental status may be presenting symptoms. The diagnosis is usually made presumptively based on the characteristic appearance of cerebral imaging studies in an individual known to be seropositive for *Toxoplasma*. Typically, toxoplasmosis appears as multiple contrast-enhancing lesions on CT scan. Lesions tend to be peripheral, with a predilection for the basal ganglia.

Single lesions are atypical of toxoplasmosis. When a single lesion has been detected by CT scanning, MRI scanning may reveal multiple lesions because of its greater sensitivity. If a patient has a single lesion on MRI and is neurologically stable, clinicians may pursue a 2-week empiric trial of toxoplasmosis therapy. A repeat scan should be performed at 2 weeks. If the lesion has not diminished in size, biopsy of the lesion should be performed. A positive *Toxoplasma* serologic test does not confirm the diagnosis because many HIV-infected patients have detectable titers without having active disease.

Conversely, less than 3% of patients with toxoplasmosis have negative titers. Therefore, negative *Toxoplasma* titers in an HIV-infected patient with a space-occupying lesion should be a cause for aggressively pursuing an alternative diagnosis. The preferred treatment of toxoplasmosis is with pyrimethamine and sulfadiazine (Table 31–3). If pyrimethamine is not available, patients can be treated with trimethoprim-sulfamethoxazole.

Vidal JE. HIV-related cerebral toxoplasmosis revisited: current concepts and controversies of an old disease. *J Int Assoc Provid AIDS Care.* 2019;18:2325958219867315. [PMID: 31429353]

2. Central nervous system lymphoma—Primary non-Hodgkin lymphoma is the second most common CNS space-occupying lesion in HIV-infected patients. Symptoms are similar to those with toxoplasmosis. While imaging techniques cannot distinguish these two diseases with certainty, lymphoma more often is solitary. Other less common lesions should be suspected if there is preceding bacteremia, positive tuberculin test, fungemia, or injection drug use. These include bacterial abscesses, cryptococcosis, tuberculomas, and *Nocardia* lesions.

Stereotactic brain biopsy should be strongly considered if lesions are solitary or do not respond to toxoplasmosis treatment, especially if they are easily accessible. Diagnosis of lymphoma is important because many patients benefit from treatment (radiation therapy). Although a positive polymerase chain reaction (PCR) assay of cerebrospinal fluid for Epstein–Barr virus DNA is consistent with a diagnosis of lymphoma, the sensitivity and specificity of the test are not high enough to obviate the need for a brain biopsy.

Brandsma D et al. Primary CNS lymphoma in HIV infection. *Handb Clin Neurol.* 2018;152:177. [PMID: 29604975]
Marcus C et al. Imaging in differentiating cerebral toxoplasmosis and primary CNS lymphoma with special focus on FDG PET/CT. *AJR Am J Roentgenol.* 2021;216:157. [PMID: 33112669]

3. HIV-associated dementia and neurocognitive disorders—Patients with HIV-associated dementia typically have difficulty with cognitive tasks (eg, memory, attention), exhibit diminished motor function, and have emotional or behavioral problems. Patients may first notice a deterioration in their handwriting. The manifestations of dementia may wax and wane, with persons exhibiting periods of lucidity and confusion over the course of a day. The diagnosis of HIV-associated dementia is one of exclusion based on a brain imaging study and on spinal fluid analysis that excludes other pathogens. Neuropsychiatric testing is helpful in distinguishing patients with dementia from those with depression. Many patients improve with effective antiretroviral treatment. However, slowly progressive neurocognitive deficits may still develop in patients taking antiretroviral treatment as they age.

Metabolic abnormalities may also cause changes in mental status: hypoglycemia, hyponatremia, hypoxia, and drug overdose are important considerations in this population. Other less common infectious causes of encephalopathy include progressive multifocal leukoencephalopathy

(discussed below), CMV, syphilis, and herpes simplex encephalitis.

Avedissian SN et al. Pharmacologic approaches to HIV-associated neurocognitive disorders. *Curr Opin Pharmacol.* 2020; 54:102. [PMID: 33049585]

Rosca EC et al. Montreal Cognitive Assessment (MoCA) for HIV-associated neurocognitive disorders. *Neuropsychol Rev.* 2019;29:313. [PMID: 31440882]

4. Cryptococcal meningitis—Cryptococcal meningitis typically presents with fever and headache. Less than 20% of patients have meningismus. Diagnosis is based on a positive latex agglutination test of serum that detects cryptococcal antigen (or “CRAG”) or positive culture of spinal fluid for *Cryptococcus*. Seventy to 90% of patients with cryptococcal meningitis have a positive serum CRAG. Thus, a negative serum CRAG test makes a diagnosis of cryptococcal meningitis unlikely and can be useful in the initial evaluation of a patient with headache, fever, and normal mental status. Treatment has three phases: induction, consolidation, and maintenance. Induction treatment is given for a minimum of 2 weeks plus evidence of clinical improvement and a negative CSF culture on repeat lumbar puncture. Treatment can be stopped after 1 year of maintenance therapy if the patient is asymptomatic, has a CD4 cell count of greater than 100/mcL for at least 3 months, and has suppressed viral load on effective antiretroviral treatment. The preferred treatment is liposomal amphotericin with flucytosine (Table 31–3).

Boyer-Chammard T et al. Recent advances in managing HIV-associated cryptococcal meningitis. *F1000Res.* 2019;8:743. [PMID: 31275560]

Lawrence DS. Emerging concepts in HIV-associated cryptococcal meningitis. *Curr Opin Infect Dis.* 2019;32:16. [PMID: 30507673]

Skipper C et al. Diagnosis and management of central nervous system cryptococcal infections in HIV-infected adults. *J Fungi (Basel).* 2019;5:E65. [PMID: 31330959]

5. Meningococcal meningitis—HIV-infected persons are at increased risk for meningococcal disease. Treatment is the same as in uninfected persons. Therefore, the Advisory Committee on Immunization Practices recommends the meningococcal conjugate vaccine (serogroups A, C, W, and Y) for all HIV-infected persons aged 2 months or older.

Bozio CH et al. Meningococcal disease surveillance in men who have sex with men—United States, 2015–2016. *MMWR Morb Mortal Wkly Rep.* 2018;67:1060. [PMID: 30260947]

6. HIV meningitis and HIV myelopathy—HIV meningitis, characterized by lymphocytic pleocytosis of the spinal fluid with negative culture, is common early in HIV infection. Spinal cord function may also be impaired in HIV-infected individuals. HIV myelopathy presents with leg weakness and incontinence. Spastic paraparesis and sensory ataxia are seen on neurologic examination. Myelopathy is usually a late manifestation of HIV disease, and most patients will have concomitant HIV encephalopathy. Pathologic evaluation of the spinal cord reveals vacuolation of white matter. Because HIV

myelopathy is a diagnosis of exclusion, symptoms suggestive of myelopathy should be evaluated by lumbar puncture to rule out CMV polyradiculopathy (described below) and an MRI or CT scan to exclude epidural lymphoma.

Leffert J et al. HIV-vacuolar myelopathy: an unusual early presentation in HIV. *Int J STD AIDS.* 2021;32:205. [PMID: 33323068]

Levin SN et al. HIV and spinal cord disease. *Handb Clin Neurol.* 2018;152:213. [PMID: 29604979]

7. Progressive multifocal leukoencephalopathy (PML)

PML is a viral infection of the white matter of the brain seen in patients with very advanced HIV infection. It typically results in focal neurologic deficits such as aphasia, hemiparesis, and cortical blindness. Imaging studies are strongly suggestive of the diagnosis if they show nonenhancing white matter lesions without mass effect. Extensive lesions may be difficult to differentiate from the changes caused by HIV. Several patients have stabilized or improved after the institution of effective antiretroviral treatment, and due to wide use of antiretroviral treatment, PML is now rarely seen.

Abrão CO et al. AIDS-related progressive multifocal leukoencephalopathy. *Rev Soc Bras Med Trop.* 2020;54:e02522020. [PMID: 33338109]

Cortese I et al. Progressive multifocal leukoencephalopathy and the spectrum of JC virus-related disease. *Nat Rev Neurol.* 2021;17:37. [PMID: 33219338]

D. Peripheral Nervous System

A. PRESENTATION—Peripheral nervous system syndromes include inflammatory polyneuropathies, sensory neuropathies, and mononeuropathies.

An **inflammatory demyelinating polyneuropathy** similar to Guillain-Barré syndrome occurs in HIV-infected patients, usually prior to frank immunodeficiency. The syndrome in many cases improves with plasmapheresis, supporting an autoimmune basis of the disease. CMV can cause an ascending polyradiculopathy characterized by lower extremity weakness and a neutrophilic pleocytosis on spinal fluid analysis with a negative bacterial culture. Transverse myelitis can be seen with herpes zoster or CMV.

Peripheral neuropathy is common among HIV-infected persons. Patients typically complain of numbness, tingling, and pain in the lower extremities. Symptoms are disproportionate to findings on gross sensory and motor evaluation. Beyond HIV infection itself, the most common cause is prior antiretroviral treatment with stavudine or didanosine. Although not used commonly in Western countries, stavudine is still being used in resource-limited settings through national antiretroviral treatment programs. Caution should be used when administering these agents to patients with a history of peripheral neuropathy. Unfortunately, medication-induced neuropathy is not always reversed when the offending agent is discontinued. Patients with advanced disease may also develop peripheral neuropathy even if they have never taken antiretroviral treatment. Evaluation should rule out other causes of

sensory neuropathy such as alcoholism, thyroid disease, vitamin B₁₂ deficiency, and syphilis.

B. MANAGEMENT—Treatment of peripheral neuropathy is aimed at symptomatic relief. Patients should be initially treated with gabapentin (start at 300 mg at bedtime and increase to 300–900 mg orally three times a day) or other co-analgesics for neuropathic pain (see Chapter 5). Opioid analgesics should be avoided because the condition tends to be chronic and patients are likely to become dependent on these agents without significant improvement in their well-being.

Julian T et al. Human immunodeficiency virus-related peripheral neuropathy: a systematic review and meta-analysis. *Eur J Neurol*. 2021;28:1420. [PMID: 33226721]

E. Rheumatologic and Bone Manifestations

Arthritis, involving single or multiple joints, with or without effusion, has been commonly noted in HIV-infected patients. Involvement of large joints is most common. Although the cause of HIV-related arthritis is unknown, most patients will respond to nonsteroidal anti-inflammatory medications. Patients with a sizable effusion, especially if the joint is warm or erythematous, should have the joint aspirated, followed by culture of the fluid to rule out suppurative arthritis as well as fungal and mycobacterial disease.

Several rheumatologic syndromes, including reactive arthritis, psoriatic arthritis, sicca syndrome, and systemic lupus erythematosus, have been reported in HIV-infected patients (see Chapter 20). However, it is unclear if the prevalence is greater than in the general population. Cases of avascular necrosis of the femoral heads have been reported sporadically, generally in the setting of advanced disease with long-standing infection and in patients receiving long-term antiretroviral treatment. The etiology is not clear but is probably multifactorial in nature.

Osteoporosis and osteopenia appear to be more common in HIV-infected patients with chronic infection and perhaps associated with long-term use of antiretroviral treatment. Vitamin D deficiency appears to be quite

common among HIV-infected populations and monitoring vitamin D levels and instituting replacement therapy for detected deficiency are recommended. Bone mineral density scans for HIV-infected postmenopausal women and men over the age of 50 are also recommended.

Thomsen MT et al. Prevalence of and risk factors for low bone mineral density assessed by quantitative computed tomography in people living with HIV and uninfected controls. *J Acquir Immune Defic Syndr*. 2020;83:165. [PMID: 31929404]
Vega LE et al. Human immunodeficiency virus infection (HIV)-associated rheumatic manifestations in the pre- and post-HAART eras. *Clin Rheumatol*. 2020;39:2515. [PMID: 32297034]

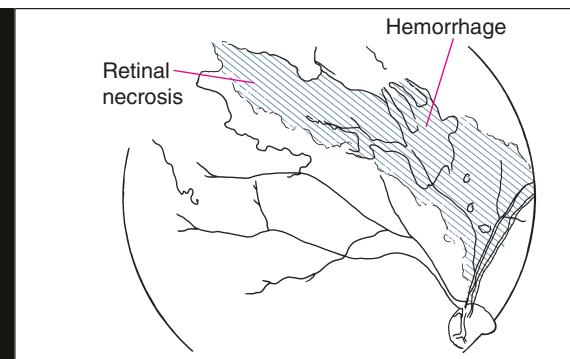
F. Myopathy

Myopathies are infrequent in the era of effective antiretroviral treatment but can be related to either HIV infection or antiretroviral treatment, particularly with use of zidovudine (azidothymidine [AZT]). Proximal muscle weakness is typical, and patients may have varying degrees of muscle tenderness. Given its long-term toxicities, zidovudine is no longer recommended when alternative treatments are available.

Kaku M et al. Neuromuscular complications of HIV infection. *Handb Clin Neurol*. 2018;152:201. [PMID: 29604977]
Prior DE et al. Neuromuscular diseases associated with human immunodeficiency virus infection. *J Neurol Sci*. 2018;387:27. [PMID: 29571868]

G. Retinitis

In HIV-infected patients, complaints of visual changes must be evaluated immediately by an ophthalmologist familiar with the manifestations of HIV disease. **CMV retinitis**, characterized by perivasculär hemorrhages and white fluffy exudates, is the most common retinal infection in AIDS patients and can be rapidly progressive (Figure 31-4). In contrast, cotton wool spots, which are also common in HIV-infected patients, are benign, remit spontaneously, and appear as small indistinct white spots without



▲ **Figure 31-4. CMV retinitis.** Retina has classic “pizza pie” or “cheese and ketchup” appearance, with hemorrhages and dirty white, granular appearing retinal necrosis adjacent to major vessels (see diagrammatic map). (Photo used, with permission, from Richard E. Wyszynski, MD. Diagram used, with permission, from Knoop KJ, Stack LB, Storrow AB, Thurman RJ. *The Atlas of Emergency Medicine*, 5th ed. McGraw Hill, 2021.)

exudation or hemorrhage. Other rare retinal processes include other herpesvirus infections or toxoplasmosis. Choice of treatment for CMV retinitis (Table 31–3) depends on severity and location of lesions, and the patient's overall condition and circumstances.

- Ballard B et al. CMV retinitis. EyeWiki. 2020 Oct 22. https://eyewiki.org/CMV_Retinitis#General_treatment
- Heiden D et al. Active cytomegalovirus retinitis after the start of antiretroviral therapy. Br J Ophthalmol. 2019;103:157. [PMID: 30196272]
- Tang Y et al. Clinical features of cytomegalovirus retinitis in HIV-infected patients. Front Cell Infect Microbiol. 2020;10:136. [PMID: 32318357]
- Wons J et al. HIV-induced retinitis. Ocul Immunol Inflamm. 2020;28:1259. [PMID: 32966142]

H. Oral Lesions

A. PRESENTATION—Oral candidiasis can be bothersome to patients, many of whom report an unpleasant taste or mouth dryness. The two most common forms of oral candidiasis seen are pseudomembranous (removable white plaques) and erythematous (red friable plaques). **Angular cheilitis**—fissures at the sides of the mouth—is usually due to *Candida* as well.

Hairy leukoplakia is caused by the Epstein-Barr virus. The lesion is not usually troubling to patients and sometimes regresses spontaneously. Hairy leukoplakia is commonly seen as a white lesion on the lateral aspect of the tongue. It may be flat or slightly raised, is usually corrugated, and has vertical parallel lines with fine or thick (“hairy”) projections (Figure 8–6).

The presence of oral candidiasis or hairy leukoplakia is significant for several reasons. First, these lesions are highly suggestive of HIV infection in patients who have no other obvious cause of immunodeficiency. Second, several studies have indicated that patients with candidiasis have a high rate of progression to AIDS even with statistical adjustment for CD4 count.

Gingival disease is common in HIV-infected patients and is thought to be due to an overgrowth of microorganisms. **Aphthous ulcers** are painful and may interfere with eating.

Other lesions seen in the mouths of HIV-infected patients include **Kaposi sarcoma** (usually on the hard palate) and **warts**.

B. MANAGEMENT—Treatment of oral candidiasis is with topical agents such as clotrimazole 10-mg troches (one troche four or five times a day). Patients with candidiasis who do not respond to topical antifungals can be treated with fluconazole (50–100 mg orally once a day for 3–7 days). Angular cheilitis can be treated topically with ketoconazole cream (2%) twice a day.

Gingival disease usually responds to professional dental cleaning and chlorhexidine rinses. A particularly aggressive gingivitis or periodontitis will develop in some HIV-infected patients; these patients should be given antibiotics that cover anaerobic oral flora (eg, metronidazole, 250 mg four times a day for 4 or 5 days) and referred to oral surgeons with experience with these entities.

Aphthous ulcers can be treated with fluocinonide (0.05% ointment mixed 1:1 with plain Orabase and applied

six times a day to the ulcer). For lesions that are difficult to reach, patients should use dexamethasone swishes (0.5 mg in 5 mL elixir three times a day). The pain of the ulcers can be relieved with use of an anesthetic spray (10% lidocaine).

Abdelwahed Hussein MR. Non-Hodgkin's lymphoma of the oral cavity and maxillofacial region: a pathologist viewpoint. Expert Rev Hematol. 2018;11:737. [PMID: 30058399]

Indrastiti RK et al. Oral manifestations of HIV: can they be an indicator of disease severity? (A systematic review). Oral Dis. 2020;26:133. [PMID: 32862546]

Tappuni AR. The global changing pattern of the oral manifestations of HIV. Oral Dis. 2020;26:22. [PMID: 32862536]

I. Gastrointestinal Manifestations

1. Candidal and other esophagitis—(See also Chapter 15.) Esophageal candidiasis is a common AIDS complication. In a patient with characteristic symptoms, empiric antifungal treatment is begun with fluconazole (100–200 mg orally daily for 14–21 days). Improvement in symptoms should be apparent within 1–2 days of antifungal treatment. If there is no improvement, further evaluation to identify other causes of esophagitis (herpes simplex, CMV) is recommended.

Hoversten P et al. Risk factors, endoscopic features, and clinical outcomes of cytomegalovirus esophagitis based on a 10-year analysis at a single center. Clin Gastroenterol Hepatol. 2020;18:736. [PMID: 31077832]

Mohamed AA et al. Diagnosis and treatment of esophageal candidiasis: current updates. Can J Gastroenterol Hepatol. 2019; 2019:3585136. [PMID: 31772927]

2. Hepatic disease

A. PRESENTATION—Autopsy studies have demonstrated that the liver is a frequent site of infections and neoplasms in HIV-infected patients. However, many of these infections are not clinically symptomatic. Mild elevations of alkaline phosphatase and aminotransferases are often noted on routine chemistry panels. **Mycobacterial disease, CMV, hepatitis B virus, hepatitis C virus, and lymphoma** cause liver disease and can present with varying degrees of nausea, vomiting, right upper quadrant abdominal pain, and jaundice. Sulfonamides, imidazole medications, antituberculous medications, pentamidine, clarithromycin, and didanosine have also been associated with hepatitis. All nucleoside reverse transcriptase inhibitors cause lactic acidosis, which can be fatal. Lactic acidosis, however, occurs most commonly when didanosine is used with stavudine; this combination is no longer recommended in antiretroviral treatment regimens. HIV-infected patients with chronic hepatitis may have more rapid progression of liver disease because of the concomitant immunodeficiency or hepatotoxicity of antiretroviral treatment. Percutaneous liver biopsy may be helpful in diagnosing liver disease, but some common causes of liver disease (eg, *M avium* complex, lymphoma) can be determined by less invasive measures (eg, blood culture, biopsy of a more accessible site).

B. MANAGEMENT—With patients living longer as a result of advances in antiretroviral treatment, advanced liver disease and hepatic failure due to chronic active hepatitis B

and/or C are increasing causes of morbidity and mortality. HIV-infected individuals who are coinfected with hepatitis B should be treated with antiretroviral regimens that include medications with activity against both viruses (tenofovir disoproxil fumarate [TDF] or tenofovir alafenamide [TAF], lamivudine, or emtricitabine). Entecavir may be used if HIV viral load is suppressed; otherwise, its use can lead to lamivudine/emtricitabine-resistant HIV. It is important to be extremely cautious about discontinuing these medications in coinfected patients as sudden discontinuation could lead to a fatal flare of hepatitis B infection.

Hepatitis C is more virulent in persons with HIV and should be treated using the new HCV direct-acting antivirals (Table 16–6). Prior to treatment, the patient's HCV viral load and HCV genotype should be determined. Depending on the genotype and the proposed treatment regimen, HCV resistance testing is recommended. For example, HCV resistance testing is recommended for patients with genotype 1a (the most common hepatitis C genotype in the United States) who are being considered for treatment with elbasvir/grazoprevir because substitutions in certain amino acid positions confer resistance. Because the appropriate treatment regimen depends on genotype, resistance profile, whether the patient is treatment naïve or not, as well as whether or not the patient has cirrhosis (and, if so, whether it is compensated or decompensated), clinicians should check the guidelines of the AASLD/IDSA (see website in references below) to see the recommended regimens (see also Tables 16–6 and 16–7). Costs of the different regimens vary by purchaser, and many clinicians choose the least expensive of the recommended regimens.

Although the recommended regimens are the same for HIV-infected patients, potential drug interactions with antiretroviral treatment may complicate treatment. Clinicians should check the guidelines of the AASLD/IDSA and US Department of Health and Human Services or the guidelines of the University of Liverpool to determine interactions between proposed hepatitis C regimen and HIV regimen.

Liver transplants have been performed successfully in HIV-infected patients. This strategy is most likely to be successful in persons who have CD4 counts greater than 100 cells/mcL and nondetectable viral loads.

Patel SV et al. Real-world efficacy of direct acting antiviral therapies in patients with HIV/HCV. *PLoS One*. 2020;15:e0228847. [PMID: 32053682]

University of Liverpool. HEP drug interactions. <https://www.hep-druginteractions.org>

Wyles DL. Antiretroviral effects on HBV/HIV co-infection and the natural history of liver disease. *Clin Liver Dis*. 2019;23:473. [PMID: 31266621]

disproportionate to elevation of the aminotransferases. Although dilated ducts can be seen on ultrasound, the diagnosis is made by endoscopic retrograde cholangiopancreatography, which reveals intraluminal irregularities of the proximal intrahepatic ducts with “pruning” of the terminal ductal branches. Stenosis of the distal common bile duct at the papilla is commonly seen. CMV, *Cryptosporidium*, and microsporidia are thought to play inciting roles in this syndrome, but these conditions are rarely seen unless the patient is suffering with very advanced HIV-related immunodeficiency.

Naseer M et al. Epidemiology, determinants, and management of AIDS cholangiopathy: a review. *World J Gastroenterol*. 2018;24:767. [PMID: 29467548]

Velásquez JN et al. Multimethodological approach to gastrointestinal microsporidiosis in HIV-infected patients. *Acta Parasitol*. 2019;64:658. [PMID: 31286356]

4. Enterocolitis

A. PRESENTATION—**Enterocolitis** is a common problem in HIV-infected individuals. Organisms known to cause enterocolitis include bacteria (*Campylobacter*, *Salmonella*, *Shigella*), viruses (CMV, adenovirus, SARS-CoV-2), and protozoans (*Cryptosporidium*, *Entamoeba histolytica*, *Giardia*, *Isospora*, microsporidia). HIV itself may cause enterocolitis. Several of the organisms causing enterocolitis in HIV-infected individuals also cause diarrhea in immunocompetent persons. However, HIV-infected patients tend to have more severe and more chronic symptoms, including high fevers and severe abdominal pain that can mimic acute abdominal catastrophes. Bacteremia and concomitant biliary involvement are also more common with enterocolitis in HIV-infected patients. Relapses of enterocolitis following adequate therapy have been reported with both *Salmonella* and *Shigella* infections.

Because of the wide range of agents known to cause enterocolitis, a stool culture and multiple stool examinations for ova and parasites (including modified acid-fast staining for *Cryptosporidium*) should be performed. Those patients who have *Cryptosporidium* in one stool with improvement in symptoms in less than 1 month should not be considered to have AIDS, as *Cryptosporidium* is a cause of self-limited diarrhea in HIV-negative persons. More commonly, HIV-infected patients with *Cryptosporidium* infection have persistent enterocolitis with profuse watery diarrhea.

B. MANAGEMENT—To date, no consistently effective treatments have been developed for *Cryptosporidium* infection except to improve immune function through the use of effective antiretroviral treatment. The diarrhea can be treated symptomatically with diphenoxylate with atropine (one or two tablets orally three or four times a day). Those who do not respond may be given paregoric with bismuth (5–10 mL orally three or four times a day). Octreotide in escalating doses (starting at 0.05 mg subcutaneously every 8 hours for 48 hours) has been found to ameliorate symptoms in approximately 40% of patients with cryptosporidia, although the benefit is often short-lived.

Patients with a negative stool examination and persistent symptoms should be evaluated with colonoscopy and

3. Biliary disease—**Cholecystitis** presents with manifestations similar to those seen in immunocompetent hosts but is more likely to be acalculous. **Sclerosing cholangitis** and **papillary stenosis** have also been reported in HIV-infected patients. Typically, the syndrome presents with severe nausea, vomiting, and right upper quadrant pain. Liver enzymes generally show alkaline phosphatase elevations

biopsy. Patients whose symptoms last longer than 1 month with no identified cause of diarrhea are considered to have a presumptive diagnosis of **AIDS enteropathy**. Patients may respond to institution of effective antiretroviral treatment or octreotide. Upper endoscopy with small bowel biopsy is not recommended as a routine part of the evaluation.

Wang RJ et al. Widespread occurrence of *Cryptosporidium* infections in patients with HIV/AIDS: epidemiology, clinical feature, diagnosis, and therapy. *Acta Trop.* 2018;187:257. [PMID: 30118699]

Wang ZD et al. Prevalence of *Cryptosporidium*, microsporidia and *Isospora* infection in HIV-infected people: a global systematic review and meta-analysis. *Parasit Vectors.* 2018;11:28. [PMID: 29316950]

5. Other disorders—Two other important gastrointestinal abnormalities in HIV-infected patients are **gastropathy** and malabsorption. It has been documented that some HIV-infected patients do not produce normal levels of stomach acid and therefore are unable to absorb medications that require an acid medium. This decreased acid production may explain, in part, the susceptibility of HIV-infected patients to *Campylobacter*, *Salmonella*, and *Shigella*, all of which are sensitive to acid concentration. There is no evidence that *Helicobacter pylori* is more common in HIV-infected persons.

A **malabsorption** syndrome occurs commonly in AIDS patients. It can be due to infection of the small bowel with *M avium* complex, *Cryptosporidium*, or microsporidia.

Hall VP. Common gastrointestinal complications associated with human immunodeficiency virus/AIDS: an overview. *Crit Care Nurs Clin North Am.* 2018;30:101. [PMID: 29413205]

J. Endocrinologic Manifestations

Hypogonadism is probably the most common endocrinologic abnormality in HIV-infected men. The adrenal gland is also a commonly afflicted endocrine gland in patients with AIDS. Abnormalities demonstrated on autopsy include infection (especially with CMV and *M avium* complex), infiltration with Kaposi sarcoma, and injury from hemorrhage and presumed autoimmunity. The prevalence of clinically significant adrenal insufficiency is low. Patients with suggestive symptoms should undergo a cosyntropin stimulation test.

Although frank deficiency of cortisol is rare, an isolated defect in mineralocorticoid metabolism may lead to salt-wasting and hyperkalemia. Such patients should be treated with fludrocortisone (0.1–0.2 mg orally daily).

AIDS patients appear to have abnormalities of thyroid function tests different from those of patients with other chronic diseases. AIDS patients have been shown to have high levels of triiodothyronine (T_3), thyroxine (T_4), and thyroid-binding globulin and low levels of reverse triiodothyronine (rT_3). The causes and clinical significance of these abnormalities are unknown.

Mirza FS et al. Endocrinological aspects of HIV infection. *J Endocrinol Invest.* 2018;41:881. [PMID: 29313284]

Pezzaioli LC et al. The importance of SHBG and calculated free testosterone for the diagnosis of symptomatic hypogonadism in HIV-infected men: a single-centre real-life experience. *Infection.* 2021;49:295. [PMID: 33289905]

Zaid D et al. Human immunodeficiency virus infection and the endocrine system. *Endocrinol Metab (Seoul).* 2019;34:95. [PMID: 31257738]

K. Skin Manifestations

The skin manifestations that commonly develop in HIV-infected patients can be grouped into viral, bacterial, fungal, neoplastic, and nonspecific dermatitides.

Coates SJ et al. What's new in HIV dermatology? *F1000Res.* 2019;8:980. [PMID: 31297183]

1. Viral dermatitides

A. HERPES SIMPLEX INFECTIONS—These infections (Figure 31-5) occur more frequently, tend to be more severe, and are more likely to disseminate in AIDS patients than in immunocompetent persons. Because of the risk of progressive local disease, all herpes simplex attacks should be treated for 5–10 days with acyclovir (400 mg orally three times a day), famciclovir (500 mg orally twice daily), or valacyclovir (500 mg orally twice daily) (Table 31-3). To avoid the complications of attacks, many clinicians recommend suppressive therapy for HIV-infected patients with a history of recurrent herpes. Options for suppressive therapy include acyclovir (400 mg orally twice daily), famciclovir (250 mg orally twice daily), and valacyclovir (500 mg orally daily). Long-term suppressive herpes prophylaxis with acyclovir does not reduce HIV transmission between heterosexual men and women from developing countries.

B. HERPES ZOSTER—This is a common manifestation of HIV infection. Patients with herpes zoster infections



▲ Figure 31-5. Herpes simplex viral skin infection, frequently found in HIV-positive men. Shown are grouped vesicles typical of herpes simplex on the penis, with both intact vesicles of initial eruption and visible crusts of resolving lesions. (Reproduced, with permission, from Eric Kraus, MD, in: Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

should be treated for 7–10 days with famciclovir (500 mg orally three times a day) or valacyclovir (500 mg three times a day). Acyclovir can also be used, but it requires very frequent dosing (800 mg orally four or five times per day for 7 days). Vesicular lesions should be cultured if there is any question about their origin, since herpes simplex responds to much lower doses of acyclovir. Disseminated zoster and cases with ocular involvement should be treated with intravenous (10 mg/kg every 8 hours for 7–10 days) rather than oral acyclovir. The recombinant zoster vaccine (Shingrix, two doses administered 2–6 months apart) can be given to HIV-infected patients. Because it is not a live virus like the previous zoster vaccine (Zostavax), it is not contraindicated in patients with immune deficiency but, based on other vaccines, HIV-infected patients are likely to develop more robust immune response to the vaccine when their CD4 count is greater than 200/mcL. The long-term benefit of Shingrix in preventing shingles in HIV-infected persons has yet to be established.

Dooling KL et al. Recommendations of the Advisory Committee on Immunization Practices for use of herpes zoster vaccines. MMWR Morb Mortal Wkly Rep. 2018;67:103. [PMID: 29370152]
 James SF et al. Shingrix: the new adjuvanted recombinant herpes zoster vaccine. Ann Pharmacother. 2018;52:673. [PMID: 29457489]

c. MOLLUSCUM CONTAGIOSUM—This infection is caused by a pox virus and is seen in HIV-infected patients, as in other immunocompromised patients. The characteristic umbilicated fleshy papular lesions have a propensity for spreading widely over the patient's face and neck (Figure 31–6) and should be treated with topical liquid nitrogen.

Murphy M et al. Non-HPV perianal and anorectal sexually transmitted viral infections. Clin Colon Rectal Surg. 2019;32:340. [PMID: 31507343]



▲ **Figure 31–6. Molluscum contagiosum.** Extensive molluscum contagiosum lesions on the face of a young woman, suggestive she may be HIV-positive. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

2. Bacterial dermatitides

A. STAPHYLOCOCCAL INFECTION—*Staphylococcus* is the most common bacterial cause of skin disease in HIV-infected patients; it usually presents as **folliculitis**, **superficial abscesses (furuncles)**, or **bullous impetigo**. These lesions should be treated aggressively since sepsis can occur. Folliculitis is initially treated with topical clindamycin or mupirocin, and patients may benefit from regular washing with an antibacterial soap such as chlorhexidine. Intranasal mupirocin has been used successfully for staphylococcal decolonization in other settings. In HIV-infected patients with recurrent staphylococcal infections, weekly intranasal mupirocin should be considered in addition to topical care and systemic antibiotics. Abscesses often require incision and drainage. Patients may need anti-staphylococcal antibiotics as well. Due to high frequency of methicillin-resistant *Staphylococcus aureus* (MRSA) skin infections in HIV-infected populations, lesions should be cultured prior to initiating empiric antistaphylococcal therapy. Recommendations for empiric treatment are either (1) trimethoprim-sulfamethoxazole (one double-strength tablet orally twice daily) with or without clindamycin (500 mg orally three times daily); or (2) doxycycline (100 mg orally twice daily) with close follow-up.

Hatlen TJ et al. Staphylococcal skin and soft tissue infections. Infect Dis Clin North Am. 2021;35:81. [PMID: 33303329]
 Sabbagh P et al. The global and regional prevalence, burden, and risk factors for methicillin-resistant *Staphylococcus aureus* colonization in HIV-infected people: a systematic review and meta-analysis. Am J Infect Control. 2019;47:323. [PMID: 30170767]

B. BACILLARY ANGIOMATOSIS—It is caused by two closely related organisms: *Bartonella henselae* and *Bartonella quintana*. The epidemiology of these infections suggests zoonotic transmission from fleas of infected domestic cats. The most common manifestation is raised, reddish, highly vascular skin lesions that can mimic lesions of Kaposi sarcoma. Fever is a common manifestation of this infection; involvement of bone, lymph nodes, and liver has also been reported. The infection responds to doxycycline, 100 mg orally twice daily, or erythromycin, 250 mg orally four times daily for at least 14 days. Patients who are seriously ill with visceral involvement may require months of therapy.

Mantis J et al. Cat-scratch disease in an AIDS patient presenting with generalized lymphadenopathy: an unusual presentation with delayed diagnosis. Am J Case Rep. 2018;19:906. [PMID: 30068900]

3. Fungal rashes

A. RASHES DUE TO DERMATOPHYTES AND CANDIDA—Most **fungal rashes** afflicting AIDS patients are due to dermatophytes and *Candida*. While particularly common in the inguinal region, they may occur anywhere on the body. Fungal rashes generally respond well to topical clotrimazole (1% cream twice a day) or ketoconazole (2% cream twice a day).

B. SEBORRHEIC DERMATITIS—This is more common in HIV-infected patients. Scrapings of seborrhea have revealed *Malassezia furfur* (*Pityrosporum ovale*), implying that the seborrhea is caused by this fungus. A consistent finding is that seborrhea responds well to topical clotrimazole (1% cream) as well as hydrocortisone (1% cream).

Moreno-Coutiño G et al. Isolation of *Malassezia* spp. in HIV-positive patients with and without seborrheic dermatitis. *An Bras Dermatol.* 2019;94:527. [PMID: 31777352]
Wikramanayake TC et al. Seborrheic dermatitis—looking beyond *Malassezia*. *Exp Dermatol.* 2019;28:991. [PMID: 31310695]

4. Neoplastic dermatitides—See Chapter 6 and the Kaposi sarcoma section below.

5. Nonspecific dermatitides

A. XEROSIS—This condition presents in HIV-infected patients with severe pruritus. The patient may have no rash, or nonspecific excoriations from scratching. Treatment is with emollients (eg, absorption base cream) and antipruritic lotions (eg, camphor 9.5% and menthol 0.5%).

B. PSORIASIS—Psoriasis can be very severe in HIV-infected patients. Phototherapy and etretinate (0.25–9.75 mg/kg/day orally in divided doses) may be used for recalcitrant cases in consultation with a dermatologist.

L. HIV-Related Malignancies

Four cancers are currently included in the CDC classification of AIDS: Kaposi sarcoma, non-Hodgkin lymphoma, primary lymphoma of the brain, and invasive cervical carcinoma. Epidemiologic studies have shown that between 1973 and 1987, among single men in San Francisco, the risk of Kaposi sarcoma increased more than 5000-fold and the risk of non-Hodgkin lymphoma more than 10-fold. The increase in incidence of malignancies is probably a function of impaired cell-mediated immunity. In the current treatment era, cancers not classified as AIDS-related, such as lung cancer, are being increasingly diagnosed in aging HIV-infected individuals despite optimal antiretroviral treatment. Cohort studies suggest that HIV-infected adults are at increased risk for a variety of cancers compared to age-matched uninfected populations. Mortality secondary to malignancies represents an increasing cause of death in HIV-infected populations.

Hessol NA et al. Incidence of first and second primary cancers diagnosed among people with HIV, 1985–2013: a population-based, registry linkage study. *Lancet HIV.* 2018;5:e647. [PMID: 30245004]

Shiels MS et al. Projected cancer incidence rates and burden of incident cancer cases in HIV-infected adults in the United States through 2030. *Ann Intern Med.* 2018;168:866. [PMID: 29801099]

Valanikas E et al. Cancer prevention in patients with human immunodeficiency virus infection. *World J Clin Oncol.* 2018;9:71. [PMID: 30254961]

Vangipuram R et al. AIDS-associated malignancies. *Cancer Treat Res.* 2019;177:1. [PMID: 30523619]

1. Kaposi sarcoma

A. PRESENTATION—Lesions may appear anywhere; careful examination of the eyelids, conjunctiva, pinnae, palate, and toe webs is mandatory to locate potentially occult lesions. In light-skinned individuals, Kaposi lesions usually appear as purplish, nonblanching lesions that can be papular or nodular. In dark-skinned individuals, the lesions may appear browner. In the mouth, lesions are most often palatal papules, though exophytic lesions of the tongue and gingivae may also be seen. Kaposi lesions may be confused with other vascular lesions such as angiomas and pyogenic granulomas. Kaposi sarcoma lesions can occur shortly after initiating antiretroviral treatment, especially in patients starting antiretroviral treatment who have advanced immunodeficiency. In this situation, Kaposi sarcoma is likely to be an immune reconstitution reaction (see Inflammatory Reactions below). Kaposi sarcoma can also cause visceral disease (eg, gastrointestinal, pulmonary).

B. MANAGEMENT—Patients with mild to moderate forms of Kaposi sarcoma do not require specific treatment as the lesions usually resolve with effective antiretroviral treatment. However, it should be noted that the lesions may flare when antiretroviral treatment is first initiated—probably as a result of an immune reconstitution process. Advanced disease is treated with combination chemotherapy (Table 31–3).

Dalla Pria A et al. Recent advances in HIV-associated Kaposi sarcoma. *F1000Res.* 2019;8:970. [PMID: 31297181]

Ngalamika O et al. Antiretroviral therapy for HIV-associated cutaneous Kaposi's sarcoma: clinical, HIV-related, and sociodemographic predictors of outcome. *AIDS Res Hum Retroviruses.* 2021;37:368. [PMID: 3386064]

2. Non-Hodgkin lymphoma

A. PRESENTATION—Non-Hodgkin lymphomas in HIV-infected persons tends to be very aggressive. These malignancies are usually of B cell origin and characterized as diffuse large-cell tumors. Over 70% of the malignancies are extranodal.

B. MANAGEMENT—The prognosis of patients with systemic non-Hodgkin lymphoma depends primarily on the degree of immunodeficiency at the time of diagnosis. Patients with high CD4 counts do markedly better than those diagnosed at a late stage of illness. Patients with primary central nervous system lymphoma are treated with radiation. Response to treatment is good, but prior to the availability of antiretroviral treatment, most patients died within a few months after diagnosis due to their underlying disease. Systemic disease is treated with combination chemotherapy (eg, EPOCH [etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin]) with rituximab. Granulocyte colony-stimulating factor (G-CSF; filgrastim) is used to maintain white blood counts.

Kimani SM et al. Epidemiology of haematological malignancies in people living with HIV. *Lancet HIV.* 2020;7:e641. [PMID: 32791045]

Lilly AJ et al. Human immunodeficiency virus-associated lymphoproliferative disorders. *Surg Pathol Clin.* 2019;12:771. [PMID: 31352987]

Re A et al. Early consolidation with high-dose therapy and autologous stem cell transplantation is a feasible and effective treatment option in HIV-associated non-Hodgkin lymphoma at high risk. *Bone Marrow Transplant.* 2018;53:228. [PMID: 28991244]

3. Hodgkin disease—Although Hodgkin disease is not included as part of the CDC definition of AIDS, studies have found that HIV infection is associated with a fivefold increase in the incidence of Hodgkin disease. HIV-infected persons with Hodgkin disease are more likely to have mixed cellularity and lymphocyte depletion subtypes of Hodgkin disease and to seek medical attention at an advanced stage of disease.

Perricone AJ et al. Cytodiagnostic sensitivity of fine needle aspiration biopsy for Hodgkin's lymphoma is decreased in patients with human immunodeficiency virus infection. *Acta Cytol.* 2019;63:352. [PMID: 31234174]

Re A et al. HIV and lymphoma: from epidemiology to clinical management. *Mediterr J Hematol Infect Dis.* 2019;11:e2019004. [PMID: 30671210]

4. Anal dysplasia and squamous cell carcinoma—These lesions have been strongly correlated with previous infection by human papillomavirus (HPV) and noted in both HIV-infected men and women. Although many of the infected MSM report a history of anal warts or have visible warts, a significant percentage have silent papillomavirus infection. Cytologic (using Papanicolaou smears) and papillomavirus DNA studies can easily be performed on specimens obtained by anal swab. Because of the risk of progression from dysplasia to cancer in immunocompromised patients, some experts advise annual anal cytologic examinations in all HIV-infected persons. An anal Papanicolaou smear is performed by rotating a moistened Dacron swab about 2 cm into the anal canal. The swab is immediately inserted into a cytology bottle. However, there is no evidence that screening for anal cancer with Papanicolaou smears decreases the incidence of invasive cancer.

HPV also appears to play a causative role in **cervical dysplasia** and **carcinoma** in HIV-infected women (discussed below).

Arens Y et al. Risk of invasive anal cancer in HIV-infected patients with high-grade anal dysplasia: a population-based cohort study. *Dis Colon Rectum.* 2019;62:934. [PMID: 3088979]

Cimic A et al. Importance of anal cytology and screening for anal dysplasia in individuals living with HIV with an emphasis on women. *Cancer Cytopathol.* 2019;127:407. [PMID: 31145557]

Power Foley M et al. Management of anal intraepithelial neoplasia and anal squamous cell carcinoma at a tertiary referral centre with a dedicated infectious diseases unit: an 18-year review. *Int J Colorectal Dis.* 2020;35:1855. [PMID: 32500433]

Wang CJ et al. HPV-associated anal cancer in the HIV/AIDS patient. *Cancer Treat Res.* 2019;177:183. [PMID: 30523625]

M. Gynecologic Manifestations

Vaginal candidiasis, cervical dysplasia and neoplasia, and pelvic inflammatory disease are more common in

HIV-infected women than in uninfected women. These manifestations also tend to be more severe when they occur in association with HIV infection. Therefore, HIV-infected women need frequent gynecologic care. **Vaginal candidiasis** may be treated with topical agents or a single dose of oral fluconazole (150 mg) (see Chapter 36). Recurrent vaginal candidiasis should be treated with fluconazole (100–200 mg) for at least 7 days. However, fluconazole increases the risk of spontaneous abortion and should not be given to women who are or may be pregnant.

The incidence of **cervical dysplasia** in HIV-infected women is 40%. Because of this finding, recommended screening for HIV-infected women is more extensive than for uninfected women (see Chapter 18). For women younger than age 30 years, a Papanicolaou smear should be performed within a year of the onset of sexual activity, but no later than age 21 years. If normal, Papanicolaou smears should be performed yearly. After three negative examinations, screening should be done every 3 years. HPV DNA testing of the cervical specimen is not recommended for women younger than age 30 years.

For women age 30 and older, screening should continue beyond age 65 (unlike the general population). There are two accepted screening protocols: cytology alone and cytology with HPV DNA cotesting. A Papanicolaou smear is done when HIV is diagnosed and every 12 months thereafter, and after three negative smears, ongoing screening can be performed every 3 years. Alternatively, a Papanicolaou smear with cotesting for HPV DNA can be performed when HIV is diagnosed or starting when patients are age 30 years old. If Papanicolaou smear is normal and HPV test is negative, then the next screening can be in 3 years.

The management of abnormal Papanicolaou tests and positive HPV tests is the same in infected women as in uninfected women. Treatment should follow the consensus guidelines in the references below.

While **pelvic inflammatory disease** appears to be more common in HIV-infected women, the bacteriology of this condition appears to be the same as among HIV-uninfected women. HIV-infected women with pelvic inflammatory disease should be treated with the same regimens as uninfected women (see Chapter 18).

Smith AJB et al. Gynecologic cancer in HIV-positive women: a systematic review and meta-analysis. *Am J Obstet Gynecol.* 2019;221:194. [PMID: 30771344]

Strickler HD et al. Primary HPV and molecular cervical cancer screening in US women living with HIV. *Clin Infect Dis.* 2021;72:1529. [PMID: 32881999]

N. Coronary Artery Disease

HIV-infected persons are at higher risk for coronary artery disease than age- and sex-matched controls. Part of this increase in coronary artery disease is due to changes in lipids caused by antiretroviral agents (see below), especially stavudine and several of the PIs. However, some of the risk appears to be due to HIV infection, independent of its therapy. It is important that clinicians pay close attention to this issue because myocardial infarctions tend to present at a younger age in HIV-infected individuals than in

HIV-uninfected individuals. HIV-infected patients with symptoms of coronary artery disease such as chest pain or dyspnea should be rapidly evaluated. Clinicians should aggressively treat conditions that result in increased risk of heart disease, especially smoking, hypertension, hyperlipidemia, obesity, diabetes mellitus, and sedentary lifestyle.

Bernelli C et al. Cardiovascular events recurrence and coronary artery disease in HIV patients: the price we have to pay for the chronicization of the disease. *Can J Cardiol.* 2020;36:127. [PMID: 31813674]

Hsue PY et al. HIV infection and coronary heart disease: mechanisms and management. *Nat Rev Cardiol.* 2019;16:745. [PMID: 31182833]

Patel AA et al. Coronary artery disease in patients with HIV infection: an update. *Am J Cardiovasc Drugs.* 2020. [Epub ahead of print] [PMID: 33184766]

O. Inflammatory Reactions (Immune Reconstitution Inflammatory Syndromes)

With initiation of antiretroviral treatment, some patients experience **inflammatory reactions** that appear to be associated with immune reconstitution as indicated by a rapid increase in CD4 count. These inflammatory reactions may present with generalized signs of fevers, sweats, and malaise with or without more localized manifestations that usually represent unusual presentations of opportunistic infections. For example, vitritis has developed in patients with CMV retinitis after they have been treated with antiretroviral treatment.

M avium can present as focal even suppurative lymphadenitis or granulomatous masses in patients receiving antiretroviral treatment. Tuberculosis may paradoxically worsen with new or evolving pulmonary infiltrates and lymphadenopathy. PML and cryptococcal meningitis may also behave atypically. Clinicians should be alert to these syndromes, which are most often seen in patients who have initiated antiretroviral treatment in the setting of advanced disease and who show rapid increases in CD4 counts with treatment. The diagnosis of **immune reconstitution inflammatory syndrome (IRIS)** is one of exclusion and can be made only after recurrence or new opportunistic infection has been ruled out as the cause of the clinical deterioration. Management of IRIS is conservative and supportive with use of corticosteroids only for severe reactions. Most authorities recommend that antiretroviral treatment be continued unless the IRIS reaction is life-threatening.

Sereti I. Immune reconstruction inflammatory syndrome in HIV infection: beyond what meets the eye. *Top Antivir Med.* 2020;27:106. [PMID: 32224502]

Sereti I et al. Prospective international study of incidence and predictors of immune reconstitution inflammatory syndrome and death in people living with human immunodeficiency virus and severe lymphopenia. *Clin Infect Dis.* 2020;71:652. [PMID: 31504347]

precautions regarding sexual practices and injection drug use, initiation of antiretroviral treatment as a prevention tool for transmission to others, preexposure and postexposure use of antiretroviral treatment, perinatal management including antiretroviral treatment of the mother, screening of blood products, and infection control practices in the health care setting.

1. HIV testing and counseling—Primary care clinicians should routinely obtain a sexual history and provide risk factor assessment of their patients. Because approximately 15% of the HIV-infected persons in the United States do not know they are infected, the US Preventive Services Task Force recommends that clinicians screen for HIV infection in adolescents and adults ages 15 to 65 years. Younger adolescents and older adults who are at increased risk should also be screened. Clinicians should review the risk factors for HIV infection with the patient and discuss safer sex and safer needle use as well as the meaning of a positive test. Although the CDC recommends “opt-out” testing in medical settings, some states require specific written consent. For persons whose test results are positive, it is critically important that they be connected to ongoing medical care. Many public health systems advocate for initiating care and treatment the same day that someone tests positive if appropriate resources are available (see C. Antiviral Treatment, below). Referrals for partner-notification services, social services, mental health services, and HIV-prevention services should also be provided. Prevention interventions focused on the importance of HIV-infected persons not putting others at risk have been successful.

For patients whose test results are negative, clinicians should review safer sex and needle use practices, including counseling not to exchange bodily fluids unless they are in a long-term mutually monogamous relationship with someone who has tested HIV antibody-negative and has not engaged in unsafe sex, injection drug use, or other HIV risk behaviors for at least 6 months prior to or at any time since the negative test.

To prevent sexual transmission of HIV, only latex or polyurethane condoms should be used, along with a water-soluble lubricant. Although nonoxynol-9, a spermicide, kills HIV, it is contraindicated because in some patients it may cause genital ulcers that could facilitate HIV transmission. Patients should be counseled that condoms are not 100% effective. They should be made familiar with the use of condoms, including, specifically, the advice that condoms must be used every time, that space should be left at the tip of the condom as a receptacle for semen, that intercourse with a condom should not be attempted if the penis is only partially erect, that men should hold on to the base of the condom when withdrawing the penis to prevent slippage, and that condoms should not be reused. Although anal intercourse remains the sexual practice at highest risk for transmitting HIV, seroconversions have been documented with vaginal and oral intercourse as well. Therefore, condoms should be used when engaging in these activities. Women as well as men having sex with men should understand how to use condoms to be sure that their partners are using them correctly. Partners of HIV-infected women should use latex or polyurethane barriers

► Prevention

A. Primary Prevention

Until vaccination is a reality, prevention of HIV infection will depend on HIV testing and counseling, including

such as dental dams (available at dental supply stores) to prevent direct oral contact with vaginal secretions. Several randomized trials in Africa demonstrated that male circumcision significantly reduced HIV incidence in men, but there are a number of barriers to performing widespread circumcisions among men in Africa.

Persons using injection drugs should be cautioned never to share needles or other drug paraphernalia. When sterile needles are not available, bleach does appear to inactivate HIV and should be used to clean needles.

Beksinska M et al. Male and female condoms: their key role in pregnancy and STI/HIV prevention. Best Pract Res Clin Obstet Gynaecol. 2020;66:55. [PMID: 32007451]

2. Antiretroviral treatment for decreasing transmission of HIV to others (treatment as prevention)—Besides preventing progression of HIV disease, effective antiretroviral treatment decreases the risk of HIV transmission between sexual partners. Among serodiscordant couples, stably suppressing HIV with antiretroviral treatment almost completely eliminates the risk of HIV transmission to the uninfected partner. Although HIV-negative persons in stable long-term partnerships with HIV-infected persons represent only one group of at-risk persons, increasing the use of antiretroviral treatment among the population of HIV-infected persons appears to decrease community-wide transmission of HIV. Despite major improvements in effectiveness and tolerability of antiretroviral treatment, only about 60% of HIV-infected persons in the United States are virally suppressed. Persons in whom the HIV virus has been “undetectable” for a prolonged period have virtually no chance of *sexually* transmitting HIV. Still, because of the possibility of variations in measured viral load, and not knowing whether their partners are virally suppressed, and the possibility of transmission through blood, all HIV-infected persons should practice safer sex and not share needles so as to avoid the possibility of transmitting HIV.

Cobb DA et al. Long-acting approaches for delivery of antiretroviral drugs for prevention and treatment of HIV: a review of recent research. Expert Opin Drug Deliv. 2020;17:1227. [PMID: 32552187]

Cohen MS et al. Prevention of HIV transmission and the HPTN 052 Study. Annu Rev Med. 2020;71:347. [PMID: 31652410]

Saag MS et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2020 recommendations of the International Antiviral Society—USA Panel. JAMA. 2020;324:1651. [PMID: 33052386]

3. Preexposure antiretroviral treatment prophylaxis—Several large randomized double-blind placebo-controlled trials demonstrated that administering emtricitabine/TDF (Truvada) can reduce the risk of sexual transmission of HIV among uninfected individuals at high risk for infection; one study was of HIV-negative men and transgender women who have sex with men, and two studies were of heterosexual HIV-discordant couples. Preexposure tenofovir has also been shown to reduce HIV infection among injection drug users from Thailand. In addition, real-world

studies of men who have sex with men, where adherence with emtricitabine/TDF has been high, have found **preexposure prophylaxis (PrEP)** to be highly effective in preventing HIV infection. Emtricitabine/TAF (Descovy) has also been approved for PrEP among men and transgender women. It has not been studied among cisgender women. Cabotegravir, a long-acting medication for PrEP, received approval by the US Food and Drug Administration (FDA) in 2021; it is injected every 8 weeks, has been shown to be superior to oral emtricitabine/TDF among men who have sex with men, transfeminine individuals who have sex with men, and cisgender women in sub-Saharan Africa.

Who should be prescribed PrEP is not a simple question. PrEP is best thought of as one “option” for HIV prevention, rather than as the only option. Whether it is the “best” option depends on three things: (1) the likelihood that a person will have HIV-infected partners or use the needles of infected persons, (2) whether there is a better option available to prevent HIV, and (3) the patient’s ability to take a daily medication. CDC guidelines recommend offering PrEP to persons at “substantial risk” for HIV. Risk for HIV is a combination of the likelihood of having a partner who is HIV-infected and the likelihood that the behavior (eg, type of intercourse, shared needles) transmits HIV. Men who have sex with men, and transgender males-to-females are the groups with the highest HIV seroprevalence in the United States, and they are likely to have partners who are known to be or at risk for being HIV-infected. Those who have receptive anal intercourse have the highest risk of HIV because the behavior is much more efficient at transmitting HIV than other sexual practices. Heterosexual drug users are also at high risk for HIV-infection if they do not consistently use clean needles or if they trade drugs for sex. It can be hardest to assess the risk of heterosexual non-drug users because it requires assessing the likelihood that their partners have HIV risks such as being bisexual men or using injection drugs. Factors known to increase the risk of HIV transmission and therefore make PrEP a good choice for particular groups of patients are shown in Table 31–4.

How does PrEP compare to other options for preventing HIV? Latex or polyurethane condoms are an excellent choice for preventing sexual transmission of HIV because they are inexpensive, have no side effects, and prevent other sexually transmitted diseases and pregnancy. However, for a variety of reasons, people do not always use condoms even when taught to do so. In addition, condoms break or slip on occasion, so even persons who always use condoms may want the extra protection of PrEP if they have a known HIV-infected partner. History of sexually transmitted diseases is proof of unprotected sex and increases the likelihood that PrEP is a good option for a patient.

Finally, for PrEP to be effective, patients have to be willing to take it. Maximum protection is generally reached in 7 days. Taking a double dose on the first day is recommended for men who have sex with men to shorten the time to maximum protection but would be expected to shorten the time to maximum protection in any person. Study participants who took at least four daily doses in a

Table 31–4. Recommendations for preexposure prophylaxis (PrEP) of HIV infection.

Patients for whom PrEP should definitely be considered as a good option for HIV prevention
Sexually active men who have sex with men, male-to-female transgender persons, and heterosexuals and bisexual women who are likely to have partners with HIV risks
Injection drug users
Factors that increase the likelihood that PrEP is a good option
Patient has receptive anal intercourse
Patient has a known HIV-infected partner
Patient has a history of sexually transmitted diseases
Patient has a high number of sex partners
Patient is a commercial sex worker
Patient with inconsistent or no condom use
Patient who has been incarcerated or who has partners that have been incarcerated
Patient is from or whose partners are from an area where HIV incidence is high
Patient who is sharing needles or related paraphernalia ("works")
Initial assessment before prescribing PrEP
HIV antibody test to confirm HIV negative
Symptom review to exclude primary HIV infection (eg, no history of acute illness with fever and rash in prior month)
STD tests: syphilis; gonorrhea (at risk site-specific); and chlamydia (at risk site-specific)
Serum creatinine and eGFR ¹
Confirm immunity to HBV or vaccinate if nonimmune ²
Pregnancy test
Discuss risks, including that PrEP is not 100% effective, does not protect against other STDs, and may have side effects
Counsel patients to use latex or polyurethane condoms and clean needles, in addition to PrEP
Assess illicit substance use and offer treatment, if needed
Discuss importance of adherence to daily medication
PrEP prescription
Emtricitabine/TDF (Truvada) 1 tablet orally daily, initially for 30–90 days; then for 90 days. (Double dose is recommended on day 1 for men who have sex with men but would shorten the time to therapeutic drug levels in any patient)
Emtricitabine/TAF (Descovy) 1 tablet orally daily, initially for 30–90 days; then for 90 days (men only; not tested in women)
Follow-up assessment
HIV antibody test every 3 months
Serum creatinine every 6 months
Pregnancy test every 3 months
STD tests: syphilis, gonorrhea (at risk site-specific); and chlamydia (at risk site-specific)
Assess and support daily medication adherence
Reinforce benefits of using latex or polyurethane condoms and clean needles with PrEP
Assess substance use and offer treatment, if needed

¹Emtricitabine/TDF is contraindicated if creatinine clearance < 60 mL/min.²HBV-infected persons may experience HBV reactivation and liver damage if emtricitabine/TDF is stopped.

eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; STD, sexually transmitted disease; TDF, tenofovir disoproxil fumarate.

PrEP checklists for providers and patients are available at <https://www.cdc.gov/hiv/risk/prep/index.html> (Last updated May 13, 2020).

week were protected almost as well as those who took the drug every day, indicating that missed doses do not render the treatment ineffective; however, adherence to daily dosing is the safest method for persons having ongoing risks. For patients preparing to stop PrEP, dosage should be continued for at least 2 days beyond the last exposure for men who have sex with men, and 7 days for all others.

For men who have sex with men, on-demand or event-driven PrEP has been studied and is effective for persons infrequently having sex who can follow the schedule. Emtricitabine/TDF is dosed 2-1-1: two tablets 2 to 24 hours prior to sex, and then one tablet 24 hours later, and a final tablet 24 hours after that.

Recommendations on initial and follow-up assessments are shown in Table 31–4. Emtricitabine/TDF is contraindicated for persons with kidney disease (creatinine clearance less than 60 mL/min) because of the small risk of kidney toxicity with TDF. Decreases in bone mineral density have been documented in persons taking emtricitabine/TDF for PrEP at 24 weeks; whether this decrease will have clinical significance is unknown. For men who have sex with men and have creatinine clearance less than 60 mL/min but greater than 30 mL/min, or osteoporosis/osteopenia (or at risk for these conditions), clinicians may opt to use emtricitabine/TAF although it is controversial whether TAF is less likely to cause clinically significant problems when used in PrEP.

Substantial increases in sexually transmitted diseases have also been seen in persons taking PrEP, indicating the importance of regular follow-up in patients using PrEP. Some patients are reluctant to use insurance to cover the cost of the medication for fear of revealing that they are at risk for HIV; without insurance, the cost is high. Programs are available from the medication manufacturer to cover the cost of treatment for low-income uninsured persons and to cover insurance copays for insured patients.

Chou R et al. Pre-exposure prophylaxis for the prevention of HIV infection: evidence report and systematic review for the U.S. Preventive Services Task Force. *JAMA*. 2019;321:2214. [PMID: 31184746]

Heendeniya A et al. Antiretroviral medications for the prevention of HIV infection: a clinical approach to preexposure prophylaxis, postexposure prophylaxis, and treatment as prevention. *Infect Dis Clin North Am*. 2019;33:629. [PMID: 31239092]

Hillis A et al. Pre-exposure prophylaxis (PrEP) for HIV prevention among men who have sex with men (MSM): a scoping review on PrEP service delivery and programming. *AIDS Behav*. 2020;24:3056. [PMID: 32274670]

Joseph Davey DL; PrEP in Pregnancy Working Group. Emerging evidence from a systematic review of safety of pre-exposure prophylaxis for pregnant and postpartum women: where are we now and where are we heading? *J Int AIDS Soc*. 2020;23:e25426. [PMID: 31912985]

Vanhamel J et al. The current landscape of pre-exposure prophylaxis service delivery models for HIV prevention: a scoping review. *BMC Health Serv Res*. 2020;20:704. [PMID: 32736626]

4. Postexposure prophylaxis for sexual and drug use exposures to HIV—The goal of postexposure prophylaxis is to reduce or prevent local viral replication prior to dissemination such that the infection can be aborted. Although there is no proof that administration of

antiretroviral medications following a sexual or parenteral drug use exposure reduces the likelihood of infection, there is suggestive data from animal models, perinatal experience, and a case-control study of health care workers who experienced a needle stick.

Treatment of persons who have been exposed to HIV should be within 72 hours, but sooner is better. All exposed persons should first receive HIV testing to exclude the possibility that they are already infected. If rapid tests are not available, treatment should begin pending the results of a standard HIV test.

The choice of antiretroviral agents and the duration of treatment are the same as those for exposures that occur through the occupational route; the preferred regimen is tenofovir 300 mg with emtricitabine 200 mg daily with raltegravir 400 mg twice a day. In contrast to those with occupational exposures, some individuals may present very late after exposure. Because the likelihood of success declines with length of time from HIV exposure, treatment is not recommended after more than 72 hours after exposure. In addition, because the psychosocial issues involved with postexposure prophylaxis for sexual and drug use exposures are complex, it should be offered with prevention counseling. Counseling should focus on how to prevent future exposures. Individuals with ongoing risk for HIV infection should be considered candidates for PrEP. Clinicians needing more information on postexposure prophylaxis for occupational or nonoccupational exposures should contact the National Clinicians' Post-Exposure Prophylaxis Hotline (1-888-448-4911; <http://nccc.ucsf.edu/clinician-consultation/pep-post-exposure-prophylaxis/>).

Atim M et al; Dean Street Collaborative Group. Post-exposure prophylaxis in the era of pre-exposure prophylaxis. *HIV Med.* 2020;21:668. [PMID: 32902098]

Centers for Disease Control and Prevention. HIV, HIV Basics, Prevention, PEP (Post-Exposure Prophylaxis). 2020 Oct 21. <https://www.cdc.gov/hiv/basics/pep.html>

DeHaan E. Post-exposure prophylaxis (PEP) to prevent HIV infection [Internet]. Baltimore (MD): Johns Hopkins University; 2020. [PMID: 33026756]

Heedeniya A et al. Antiretroviral medications for the prevention of HIV infection: a clinical approach to preexposure prophylaxis, postexposure prophylaxis, and treatment as prevention. *Infect Dis Clin North Am.* 2019;33:629. [PMID: 31239092]

O'Connell KA et al. HIV post-exposure prophylaxis in the emergency department: an updated assessment and opportunities for HIV prevention identified. *Am J Emerg Med.* 2020; S0735-6757(20)30888-3 [PMID: 33069548]

Dettinger JC et al. Perinatal outcomes following maternal pre-exposure prophylaxis (PrEP) use during pregnancy: results from a large PrEP implementation program in Kenya. *J Int AIDS Soc.* 2019;22:e25378. [PMID: 31498563]

Joseph Davey DL et al; PrEP in Pregnancy Working Group. Emerging evidence from a systematic review of safety of pre-exposure prophylaxis for pregnant and postpartum women: where are we now and where are we heading? *J Int AIDS Soc.* 2020;23:e25426. [PMID: 31912985]

6. Prevention of HIV transmission in health care settings—

In health care settings, universal body fluid precautions should be used, including use of gloves when handling body fluids and the addition of gown, mask, and goggles for procedures that may result in splash or droplet spread, and use of specially designed needles with sheath devices to decrease the risk of needle sticks. Because transmission of tuberculosis and the SARS-CoV-2 virus may occur in health care settings, all patients with cough should be encouraged to wear masks. Hospitalized HIV-infected patients with cough should be placed in respiratory isolation until tuberculosis and COVID-19 can be excluded by chest radiograph, sputum smear examination, and nasopharyngeal swab testing.

Epidemiologic studies show that needle sticks occur commonly among health care professionals, especially among surgeons performing invasive procedures, inexperienced hospital housestaff, and medical students. Efforts to reduce needle sticks should focus on avoiding recapping needles and use of safety needles whenever doing invasive procedures under controlled circumstances. The risk of HIV transmission from a needle stick with blood from an HIV-infected patient is about 1:300. The risk is higher with deep punctures, large inoculum, and source patients with high viral loads. The risk from mucous membrane contact is too low to quantitate.

Health care professionals who sustain needle sticks should be counseled and offered HIV testing as soon as possible. HIV testing is done to establish a negative baseline for worker's compensation claims in case there is a subsequent conversion. Follow-up testing is usually performed at 6 weeks, 3 months, and 6 months. With the patient's permission, their blood can be tested for HIV antibody and HIV viral load.

A case-control study by the CDC indicates that administration of zidovudine following a needle stick decreases the rate of HIV seroconversion by 79%. Therefore, clinicians should be offered antiretroviral treatment as soon as possible after exposure and continued for 4 weeks. The preferred regimen is TDF 300 mg with emtricitabine 200 mg (Truvada) daily with raltegravir 400 mg twice a day. Clinicians who have exposures to persons who are likely to have antiretroviral medication resistance (eg, persons receiving therapy who have detectable viral loads) should have their therapy individualized, using at least two medications to which the source is unlikely to be resistant. Because reports have noted hepatotoxicity due to nevirapine in this setting, this agent should be avoided. Unfortunately, there have been documented cases of seroconversion following potential parenteral exposure to HIV despite prompt use of zidovudine prophylaxis. Counseling of the clinician should include "safer sex" guidelines.

5. Prevention of perinatal transmission of HIV—Prevention of perinatal transmission of HIV begins by offering HIV counseling and testing to all women who are pregnant or considering pregnancy. HIV-infected women who are pregnant should start antiretroviral treatment with at least three medications. Recommended regimens are zidovudine and lamivudine with either ritonavir-boosted lopinavir or ritonavir-boosted atazanavir. Cesarean delivery should be planned if HIV viral load is greater than 1000 copies/mL near the time of delivery. Zidovudine should be given to the infant after birth for 6 weeks. When possible, breastfeeding should be avoided.

Centers for Disease Control and Prevention. Human Immunodeficiency Virus (HIV) and Occupational Exposure. September 5, 2019. <https://www.cdc.gov/hiv/workplace/healthcareworkers.html>

7. Prevention of transmission of HIV through blood or blood products—Current efforts in the United States to screen blood and blood products have lowered the risk of HIV transmission with transfusion of a unit of blood to 1:1,000,000. Use of blood and blood products should be judicious, with patients receiving the least amount necessary, and patients should be encouraged to donate their own blood prior to elective procedures.

8. HIV vaccine—Primate model data have suggested that development of a protective vaccine may be possible, but clinical trials in humans have been disappointing. Only one vaccine trial has shown any degree of efficacy. In this randomized, double-blind, placebo-controlled trial, a recombinant canarypox vector vaccine plus two booster injections of a recombinant gp120 vaccine reduced the risk of HIV among a primarily heterosexual population in Thailand, but efficacy was too low (31%) for widespread use. A mosaic HIV vaccine resulted in a strong immune response among adult humans and protection against infection with an HIV-like virus in rhesus monkeys. The vaccine is currently being studied in a phase IIB trial in sub-Saharan Africa.

Pitisuttithum P et al. Prophylactic HIV vaccine: vaccine regimens in clinical trials and potential challenges. Expert Rev Vaccines. 2020;19:133. [PMID: 31951766]

B. Secondary Prevention

In the era prior to the development of effective antiretroviral treatment, cohort studies of individuals with documented dates of seroconversion demonstrate that AIDS developed within 10 years in approximately 50% of untreated seropositive persons. With currently available treatment, progression of disease has been markedly decreased. In addition to antiretroviral treatment, prophylactic regimens can prevent opportunistic infections and improve survival. Prophylaxis and early intervention prevent several infectious diseases, including tuberculosis and syphilis, which are transmissible to others. Recommendations for screening tests, vaccinations, and prophylaxis are listed in Table 31–5.

1. Tuberculosis—Because of the increased occurrence of tuberculosis among HIV-infected patients, all such individuals should undergo an intradermal **PPD test** or an **interferon-gamma release assay (IGRA)** blood test at baseline and yearly thereafter if they remain at risk of exposure (eg, incarcerated, living in congregate settings). Those with a positive PPD (defined for HIV-infected patients as greater than 5 mm of induration) or a positive IGRA assay (results that are reported as positive and not negative or indeterminate) should be clinically evaluated for active tuberculosis, including by a chest radiograph. Patients with an infiltrate in any location, especially if accompanied by mediastinal adenopathy, should have sputum sent for acid-fast staining. Patients with active tuberculosis should be treated as outlined in Chapter 9 (see Tables 9–14 and

9–15). Patients with a positive PPD or IGRA assay, a normal chest radiograph, or negative sputum sample for active tuberculosis infection are classified as having latent tuberculosis infection. Patients with latent tuberculosis infection who have not been previously treated for (active or latent) tuberculosis should receive once-weekly isoniazid (900 mg orally weekly for patients greater than 50 kg) and rifapentine (900 mg orally weekly for patients greater than 50 kg) for 12 weeks. Less preferred regimens are rifampin daily (10 mg/kg; maximum and usual adult dose is 600 mg orally daily) for 4 months and isoniazid daily (300 mg orally daily) for 9 months. In patients with advanced immunodeficiency, both the PPD and IGRA assay are more likely to be falsely negative or (for IGRA assay) indeterminant. Therefore, it may be worth retesting patients with initially low CD4 counts once they have received antiretroviral treatment and have immune reconstitution (CD4 count greater than or equal to 200 cells/mcL).

Khan PY et al. Transmission of drug-resistant tuberculosis in HIV-endemic settings. Lancet Infect Dis. 2019;19:e77. [PMID: 30554996]

Peters JS et al. Advances in the understanding of *Mycobacterium tuberculosis* transmission in HIV-endemic settings. Lancet Infect Dis. 2019;19:e65. [PMID: 30554995]

2. Syphilis—Because of the increased number of cases of syphilis among MSM, including those who are HIV-infected, all such men should be screened for syphilis by a rapid plasma reagent (RPR) or Venereal Disease Research Laboratories (VDRL) test every 6 months. Increases of syphilis cases among HIV-infected persons are of particular concern because these individuals are at increased risk for reactivation of syphilis and progression to tertiary syphilis despite standard treatment. Because the only widely available tests for syphilis are serologic and because HIV-infected individuals are known to have disordered antibody production, there is concern about the interpretation of these titers. This concern has been fueled by a report of an HIV-infected patient with secondary syphilis and negative syphilis serologic testing. Furthermore, HIV-infected individuals may lose fluorescent treponemal antibody absorption (FTA-ABS) reactivity after treatment for syphilis, particularly if they have low CD4 counts. Thus, in this population, a nonreactive treponemal test does not rule out a past history of syphilis. In addition, persistence of treponemes in the spinal fluid after one dose of benzathine penicillin has been demonstrated in HIV-infected patients with primary and secondary syphilis. Therefore, the CDC has recommended an aggressive diagnostic approach to HIV-infected patients with reactive RPR or VDRL tests of longer than 1-year (or unknown) duration. All such patients should have a lumbar puncture with cerebrospinal fluid cell count and cerebrospinal fluid VDRL. Those with a normal cerebrospinal fluid evaluation are treated as having late latent syphilis (benzathine penicillin G, 2.4 million units intramuscularly weekly for 3 weeks) with follow-up titers. Those with a pleocytosis or a positive cerebrospinal fluid-VDRL test are treated as having neurosyphilis (aqueous penicillin G, 2–4 million units intravenously every 4 hours, or procaine penicillin G,

Table 31–5. Health care maintenance and monitoring of HIV-infected individuals.**For all HIV-infected individuals:**

CD4 counts every 3–6 months (can decrease to every 12 months if viral load suppressed on antiretroviral treatment for 2 years and CD4 count > 300 cells/mcL)

Viral load tests every 3–6 months and 1 month following a change in therapy

Genotypic resistance testing at baseline and if viral load not fully suppressed and patient taking antiretroviral treatment

Complete blood count, chemistry profile, transaminases and total bilirubin, at baseline and every 3–6 months

Urinalysis at baseline and annually during antiretroviral treatment (every 6 months if antiretroviral treatment regimen includes TDF)

Glucose or hemoglobin A_{1c} at baseline and annually during antiretroviral treatment

Lipid panel at baseline, 4–8 weeks after starting or changing an antiretroviral treatment regimen that affects lipids, and annually for everyone over 40 years of age

PPD or interferon-gamma release assay (IGRA) at baseline and annually if at high risk for exposure to persons with active TB

INH for those with positive PPD or IGRA, normal chest radiograph, and no history of treatment for active or latent TB

RPR or VDRL at entry and periodically based on sexual activity

Toxoplasma IgG serology at baseline

Hepatitis serologies: hepatitis A antibody, hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, hepatitis C antibody

Pneumococcal vaccine

Meningococcal vaccine

Herpes zoster vaccine¹

Inactivated influenza vaccine annually in season

Hepatitis A vaccine for those without immunity to hepatitis A

Hepatitis B vaccine for those who are hepatitis B surface antigen and antibody negative. (Use 40 mcg formulation at 0, 1, and 6 months; repeat if no immunity 1 month after three-vaccine series.)

Combined tetanus, diphtheria, pertussis vaccine

Human papillomavirus vaccine for HIV-infected women age 26 years or less

Haemophilus influenzae type b vaccination

Bone mineral density monitoring for postmenopausal women and men 50 years of age or older

Papanicolaou smears annually; if three smears are negative, can switch to longer intervals (see Complications, Section M. Gynecologic Manifestations)

Consider anal swabs for cytologic evaluation

For HIV-infected individuals with CD4 < 200 cells/mcL:

Pneumocystis jirovecii prophylaxis (see Treatment, Section A. Prophylaxis for Complications of HIV Infection and Table 31–6)

For HIV-infected individuals with CD4 < 75 cells/mcL:

Mycobacterium avium complex prophylaxis (see Treatment, Section A. Prophylaxis for Complications of HIV Infection)

For HIV-infected individuals with CD4 < 50 cells/mcL:

Consider CMV prophylaxis

¹Consider in patients age > 50 years with history of varicella immunity and T cells > 200 cells/mcL.

BUN, blood urea nitrogen; CMV, cytomegalovirus; IgG, immunoglobulin G; IGRA, interferon gamma release assay; INH, isoniazid; PPD, purified protein derivative; RPR, rapid plasma reagent; TB, tuberculosis; TDF, tenofovir disoproxil fumarate; VDRL, Venereal Disease Research Laboratories.

2.4 million units intramuscularly daily, with probenecid, 500 mg four times daily, for 10 days) followed by weekly benzathine penicillin G 2.4 million units intramuscularly for 3 weeks. Some clinicians take a less aggressive approach to patients who have low titers (less than 1:8), a history of having been treated for syphilis, and a normal neurologic examination. Close follow-up of titers is mandatory if such a course is taken. For a more detailed discussion of this topic, see Chapter 34.

Ren M et al. Deciphering the serological response to syphilis treatment in men living with HIV. AIDS. 2020;34:2089. [PMID: 32773482]

3. Immunizations—HIV-infected individuals should receive immunizations as outlined in Table 31–5. Patients without evidence of hepatitis B surface antigen or surface antibody should receive hepatitis B vaccination, using the 40-mcg formulation; the higher dose is to increase the chance of developing protective immunity. If the patient

does not have immunity 1 month after the three-shot series, then the series should be repeated. HIV-infected persons should also receive the standard inactivated vaccines such as tetanus and diphtheria boosters that would be given to uninfected persons. Most live vaccines, such as yellow fever vaccine, should be avoided. Measles vaccination, while a live virus vaccine, appears relatively safe when administered to HIV-infected individuals and should be given if the patient has never had measles or been adequately vaccinated. The new recombinant adjuvanted herpes zoster vaccine (Shingrix), two doses 2–6 months apart, is recommended for HIV-infected persons with CD4 counts greater than 200 cells/mcL. However, it is not known if it is efficacious in preventing herpes zoster in this population.

Garrido HMG et al. Immunogenicity of pneumococcal vaccination in HIV infected individuals: a systematic review and meta-analysis. EClinicalMedicine. 2020;29:100576. [PMID: 33294820]

Lee JH et al. Systematic review and meta-analysis of immune response of double dose of hepatitis B vaccination in HIV-infected patients. *Vaccine*. 2020;38:3995. [PMID: 32334887]

4. Other measures—A randomized study found that multivitamin supplementation decreased HIV disease progression and mortality in HIV-infected women in Africa. However, supplementation is unlikely to be as effective in well-nourished populations.

HIV-infected individuals should be counseled with regard to the importance of practicing safer sex even with other HIV-infected persons because of the possibility of contracting a sexually transmitted disease, such as gonorrhea or syphilis. There is also the possibility of transmission of a particularly virulent or a drug-resistant strain between HIV-infected persons. Substance abuse treatment should be recommended for persons who are using recreational drugs. They should be warned to avoid consuming raw meat, eggs, or shellfish to avoid infections with *Toxoplasma*, *Campylobacter*, and *Salmonella*. HIV-infected patients should wash their hands thoroughly after cleaning cat litter or should forgo this household chore to avoid possible exposure to toxoplasmosis. To reduce the likelihood of infection with *Bartonella* species, patients should avoid activities that might result in cat scratches or bites. Although the data are not conclusive, many clinicians recommend that HIV-infected persons—especially those with low CD4 counts—drink bottled water instead of tap water to prevent cryptosporidiosis.

Because of the emotional impact of HIV infection and subsequent illness, many patients will benefit from supportive counseling.

Treatment

Treatment for HIV infection can be broadly divided into the following categories: (1) prophylaxis for opportunistic infections, malignancies, and other complications of HIV infection; (2) treatment of opportunistic infections, malignancies, and other complications of HIV infection; and (3) treatment of the HIV infection itself with combination antiretroviral treatment.

A. Prophylaxis for Complications of HIV Infection

In general, decisions about prophylaxis of opportunistic infections are based on the CD4 count, recent HIV viral load, and a history of having had the infection in the past. In the era prior to antiretroviral treatment, patients who started taking prophylactic regimens were maintained on them indefinitely. However, studies have shown that in patients with robust improvements in immune function—as measured by increases in CD4 counts above the levels that are used to initiate treatment—prophylactic regimens can safely be discontinued.

Because individuals with advanced HIV infection are susceptible to a number of opportunistic pathogens, the use of agents with activity against more than one pathogen is preferable.

1. Prophylaxis against *Pneumocystis pneumonia*—Patients with CD4 counts below 200 cells/mcL, a CD4 lymphocyte percentage below 14%, or weight loss or oral candidiasis should be offered primary prophylaxis for *Pneumocystis pneumonia*. Patients with a history of *Pneumocystis pneumonia* should receive secondary prophylaxis until their viral load is undetectable and they have maintained a CD4 count of 200 cells/mcL or more while receiving antiretroviral treatment for longer than 3 months. Regimens for *Pneumocystis* prophylaxis are given in Table 31–6.

2. Prophylaxis against *M avium complex* infection

Patients whose CD4 counts fall to below 75–100 cells/mcL should be given prophylaxis against *M avium* complex infection. Clarithromycin (500 mg orally twice daily) and azithromycin (1200 mg orally weekly) have both been shown to decrease the incidence of disseminated *M avium* complex infection by approximately 75%, with a low rate of breakthrough of resistant disease. The azithromycin regimen is generally preferred based on high compliance and low cost. Prophylaxis against *M avium* complex infection may be discontinued in patients whose CD4 counts rise above 100 cells/mcL in response to antiretroviral treatment for longer than 3 months.

Table 31–6. *Pneumocystis jirovecii* prophylaxis, in order of preference.

Medication	Dose	Side Effects	Limitations
Trimethoprim-sulfamethoxazole	One double-strength tablet three times a week to one tablet daily	Rash, neutropenia, hepatitis, Stevens-Johnson syndrome	Hypersensitivity reaction is common but, if mild, it may be possible to treat through.
Dapsone	50–100 mg orally daily or 100 mg two or three times per week	Anemia, nausea, methemoglobinemia, hemolytic anemia	Less effective than above. Glucose-6-phosphate dehydrogenase (G6PD) level should be checked prior to therapy. Check methemoglobin level after 1 month of treatment.
Atovaquone	1500 mg orally daily with a meal	Rash, diarrhea, nausea	Less effective than suspension trimethoprim-sulfamethoxazole; equal efficacy to dapsone, but more expensive.
Aerosolized pentamidine	300 mg monthly	Bronchospasm (pretreat with bronchodilators); rare reports of pancreatitis	Apical <i>P jirovecii</i> pneumonia, extrapulmonary <i>P jirovecii</i> infections, pneumothorax.

3. Prophylaxis against toxoplasmosis—Toxoplasmosis prophylaxis is desirable in patients with a positive IgG toxoplasma serology and CD4 counts below 100 cells/mcL. Trimethoprim-sulfamethoxazole (one double-strength tablet daily) offers good protection against toxoplasmosis, as does a combination of pyrimethamine, 25 mg orally once a week, plus dapsone, 50 mg orally daily, plus leucovorin, 25 mg orally once a week. A glucose-6-phosphate dehydrogenase (G6PD) level should be checked prior to dapsone therapy, and a methemoglobin level should be checked at 1 month. Prophylaxis can be discontinued when the CD4 cells have increased to greater than 200 cells/mcL for more than 3 months.

B. Treatment of Complications of HIV Infection

Treatment of common AIDS-related complications is detailed above and in Table 31–3. In the era prior to the use of antiretroviral treatment, patients required lifelong treatment for many infections, including CMV retinitis, toxoplasmosis, and cryptococcal meningitis. However, among patients who have a good response to antiretroviral treatment, maintenance therapy for some opportunistic infections can be terminated. For example, in consultation with an ophthalmologist, maintenance treatment for CMV infection can be discontinued when persons receiving antiretroviral treatment have had a sustained increase in CD4 count to greater than 100 cells/mcL for at least 3–6 months. Similar results have been observed in patients with *M avium* complex bacteremia, who have completed a year or more of therapy for *M avium* complex and have an increase in their CD4 count to 100 cells/mcL for greater than 6 months while receiving antiretroviral treatment. Cessation of secondary prophylaxis for *Pneumocystis* pneumonia is described above.

Treating patients with repeated episodes of the same opportunistic infection can pose difficult therapeutic challenges. For example, patients with second or third episodes of *Pneumocystis* pneumonia may have developed allergic reactions to standard treatments with a prior episode. Fortunately, there are several alternatives available for the treatment of *Pneumocystis* infection. Trimethoprim with dapsone and primaquine with clindamycin are two combinations that often are tolerated in patients with a prior allergic reaction to trimethoprim-sulfamethoxazole and intravenous pentamidine. Patients in whom second episodes of *Pneumocystis* pneumonia develop while taking prophylaxis tend to have milder courses.

Adjunctive treatments—Epoetin alfa (erythropoietin) is approved for use in HIV-infected patients with anemia, including those with anemia secondary to zidovudine use. As zidovudine is rarely used now, especially at high doses, the use of epoetin alfa has also decreased. An erythropoietin level less than 500 milli-units/mL should be demonstrated before starting therapy. The starting dose of epoetin alfa is 8000 units subcutaneously three times a week. Hypertension is the most common side effect.

Human G-CSF (filgrastim) and granulocyte-macrophage colony-stimulating factor (GM-CSF [sargramostim]) have been shown to increase the neutrophil counts of

HIV-infected patients. Because of the high cost of this therapy, the dosage should be closely monitored and minimized, aiming for a neutrophil count of 1000/mcL ($1.0 \times 10^9/\text{L}$). When the medication is used for indications other than cytotoxic chemotherapy, one or two doses at 5 mcg/kg per week subcutaneously are usually sufficient.

C. Antiretroviral Therapy

The availability of agents that in combination suppress HIV replication (Table 31–7) has had a profound impact on the natural history of HIV infection. Indeed, with the advent of effective antiretroviral treatment, the life expectancy of HIV-infected persons approaches that of uninfected persons when treatment is initiated early in the course of the disease and maintained.

The recognition that HIV damages the immune system from the beginning of infection, even when the damage is not easily measured by conventional tests, combined with the greater potency, the improved side-effect profile, and the decreased pill burden of modern HIV regimens, have led to the recommendation to start treatment as soon as possible for all HIV-infected persons, including patients having acute HIV infection, regardless of CD4 count. The START trial demonstrated that immediate treatment is associated with a greater than 50% reduction in risk for serious illness or death, compared to delaying treatment until the CD4 count falls below 350 cells/mcL.

Rapid initiation programs have been created, where treatment can be started on the same day that patients test positive for HIV, so patients can start receiving treatment promptly and avoid being lost to follow-up. To do this, the clinic must have sufficient resources, medical and non-medical, to help patients cope with these major events in a short time. Also, 5–20% of patients in developed countries who are treatment-naïve have a virus that is resistant to some medications; therefore, if treatment is started before the results of resistance testing are available, a nonnucleoside reverse transcriptase inhibitor (NNRTI) should not be used. Recommended regimens for initiating treatment before resistance testing results are available include (1) dolutegravir/TAF or TDF/emtricitabine (or lamivudine), (2) bictegravir/TAF/emtricitabine, or (3) boosted darunavir/TAF or TDF/emtricitabine (or lamivudine). Also, patients requiring abacavir as part of their regimen should not start treatment prior to the results of HLA-B*5701 allele testing.

Once a decision to initiate therapy has been made, several important principles should guide therapy. First, because medication resistance to antiretroviral agents develops in HIV-infected patients, a primary goal of therapy should be complete suppression of viral replication as measured by the serum viral load. Therapy that achieves undetectable viral load has been shown to provide a durable response to the therapy. Partially suppressive combinations should be avoided. Similarly, if toxicity develops, it is preferable to change the offending medication rather than reduce individual doses.

Although the HIV treatment protocol has been for three medications from at least two different classes, exceptions

Table 31–7. Antiretroviral therapy agents by class (alphabetical order within class).

Medication	Dose	Common Side Effects	Special Monitoring ¹	Cost ²	Cost/Month
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)					
Abacavir (Ziagen)	300 mg orally twice daily	Rash, fever—if occur, rechallenge may be fatal	No special monitoring	\$9.64/300 mg	\$578.56
Didanosine (Videx)	400 mg orally daily (enteric-coated capsule) for persons ≥ 60 kg 250 mg orally daily (enteric-coated capsule) for persons 30–59 kg	Peripheral neuropathy, pancreatitis, dry mouth, hepatitis	Bimonthly neurologic questionnaire for neuropathy, potassium, amylase, bilirubin, triglycerides	\$12.29/400 mg	\$368.72
Emtricitabine (Emtriva)	200 mg orally once daily	Skin discoloration palms/soles (mild)	No special monitoring	\$19.31/200 mg	\$579.38
Lamivudine (Epivir)	150 mg orally twice daily or 300 mg daily	Rash, peripheral neuropathy	No special monitoring	\$7.15/150 mg	\$429.00
Stavudine (Zerit)	40 mg orally twice daily for persons ≥ 60 kg 30 mg orally twice daily for persons < 60 kg	Peripheral neuropathy, hepatitis, pancreatitis	Monthly neurologic questionnaire for neuropathy, amylase	\$6.85/40 mg	\$410.70
Zidovudine (AZT) (Retrovir)	600 mg orally daily in two divided doses	Anemia, neutropenia, nausea, malaise, headache, insomnia, myopathy	CBC with differential 4–8 weeks after starting AZT	\$0.90/300 mg	\$54.00
Nucleotide Reverse Transcriptase Inhibitors (NRTIs)					
Tenofovir alafenamide (TAF)/emtricitabine (Descovy)	25 mg of TAF with 200 mg of emtricitabine once daily	Nephrotoxicity; hepatotoxicity (if HBsAg positive, HBV exacerbation after discontinuation); bone resorption	Creatinine at baseline, at 2–8 weeks, then every 3–6 months; urinalysis and urine glucose and protein at baseline and repeated as clinically indicated; HBsAg, liver enzymes at baseline, at 2–8 weeks, then every 3–6 months, continue for months after discontinuation; consider bone densitometry	\$77.23/tablet	\$2316.85
Tenofovir (TDF) (Viread)	300 mg orally once daily	Kidney dysfunction, bone resorption, gastrointestinal distress	Creatinine at baseline, at 2–8 weeks, then every 3–6 months; urinalysis and urine glucose and protein at baseline and repeated as clinically indicated; consider bone densitometry	\$3.65/300 mg	\$109.50
Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)					
Doravirine (Pifetro)	100 mg daily	Headache, fatigue, abdominal pain	No special monitoring	\$60.85/100 mg	\$1825.56

(continued)

Table 31–7. Antiretroviral therapy agents by class (alphabetical order within class). (continued)

Medication	Dose	Common Side Effects	Special Monitoring ¹	Cost ²	Cost/Month
Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs) (cont.)					
Efavirenz (Sustiva)	600 mg orally daily	Neurologic disturbances, rash, hepatitis	No special monitoring	\$35.77/600 mg	\$1073.18
Etravirine (Intelence)	200 mg orally twice daily	Rash, peripheral neuropathy	No special monitoring	\$14.12/100 mg	\$1693.80
Nevirapine (Viramune)	200 mg orally daily for 2 weeks, then 200 mg orally twice daily	Rash	No special monitoring	\$10.80/200 mg	\$648.00
Rilpivirine (Edurant)	25 mg daily	Depression, rash	No special monitoring	\$48.71/25 mg	\$1461.28
Protease Inhibitors (PIs)					
Atazanavir (Reyataz)	400 mg orally once daily or 300 mg atazanavir with 100 mg ritonavir daily	Hyperbilirubinemia	Bilirubin level every 3–4 months	\$25.29/200 mg or \$50.09/300 mg	\$1517.10 (plus cost of ritonavir) \$1502.70 (plus cost of ritonavir)
Atazanavir/cobicistat (Évotaz)	300 mg of atazanavir with 150 mg of cobicistat orally once daily	Hyperbilirubinemia	Bilirubin level every 3–4 months	\$64.22/tablet	\$1926.56
Darunavir/cobicistat (Prezcobix)	800 mg of darunavir and 150 mg of cobicistat orally once daily	Rash	No special monitoring	\$84.36/tablet	\$2530.82
Darunavir/ritonavir (Prezista/Norvir)	PI-experienced patients: 600 mg of darunavir and 100 mg of ritonavir orally twice daily For PI-naïve patients: 800 mg of darunavir and 100 mg of ritonavir orally daily	Rash	No special monitoring	\$36.90/600 mg (darunavir) \$73.80/800 mg (darunavir)	2214.23 (plus cost of ritonavir) \$2214.33 (plus cost of ritonavir)
Fosamprenavir (Lexiva)	For PI-experienced patients: 700 mg of fosamprenavir and 100 mg of ritonavir orally twice daily For PI-naïve patients: 1400 mg orally twice daily or 1400 mg of fosamprenavir and 200 mg of ritonavir orally once daily	Gastrointestinal, rash	No special monitoring	\$20.83/700 mg	\$1249.86/700 mg (plus cost of ritonavir) \$2499.72/1400 mg (plus cost of ritonavir)
Indinavir (Crixivan)	800 mg orally three times daily	Renal calculi	Bilirubin level every 3–4 months	\$3.05/400 mg	\$548.12
Lopinavir/ritonavir (Kaletra)	400 mg/100 mg orally twice daily	Diarrhea	No special monitoring	\$10.24/200 mg (Kaletra)	\$1228.97
Nelfinavir (Viracept)	750 mg orally three times daily or 1250 mg twice daily	Diarrhea	No special monitoring	\$4.86/250 mg or \$12.14/625 mg	\$1312.20 or \$1456.80
Ritonavir (Norvir)	600 mg orally twice daily or in lower doses (eg, 100 mg orally once or twice daily) for boosting other PIs	Gastrointestinal distress, peripheral paresthesias	No special monitoring	\$9.26/100 mg	\$3333.60 (\$277.80–555.60 in lower doses)
Saquinavir hard gel (Invirase)	1000 mg orally twice daily with 100 mg of ritonavir orally twice daily	Gastrointestinal distress	No special monitoring	\$12.02/500 mg	\$1442.09 (plus cost of ritonavir)

(continued)

Table 31–7. Antiretroviral therapy agents by class (alphabetical order within class). (continued)

Medication	Dose	Common Side Effects	Special Monitoring ¹	Cost ²	Cost/Month
Protease Inhibitors (PIs) (cont.)					
Tipranavir/ritonavir (Aptivus/Norvir)	500 mg of tipranavir and 200 mg of ritonavir orally twice daily	Gastrointestinal, rash	No special monitoring	\$18.44/250 mg (tipranavir)	\$2213.15 (plus cost of ritonavir)
Entry Inhibitors					
Enfuvirtide (Fuzeon)	90 mg subcutaneously twice daily	Injection site pain and allergic reaction	No special monitoring	\$71.71/90 mg	\$4302.67
Integrase Inhibitors					
Bictegravir	50 mg orally daily. No longer marketed as a single agent; used in antiretroviral combination (Table 31–8)	Diarrhea, nausea, headache	No special monitoring	No longer marketed as a single agent	No longer marketed as a single agent
Dolutegravir (Tivicay)	Treatment-naïve or integrase-naïve patients: 50 mg daily. When administered with efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifapentine: 50 mg twice daily. When administered to integrase-experienced patients with suspected integrase resistance: 50 mg twice daily.	Hypersensitivity, insomnia, fatigue, headache, rash	No special monitoring	\$76.67/50 mg	\$2300.04/50 mg daily or \$4600.08/50 mg twice daily
Elvitegravir	No longer marketed as a single agent; used in antiretroviral combinations (Table 31–8)	Diarrhea, headache	No special monitoring	No longer marketed as a single agent	No longer marketed as a single agent
Raltegravir (Isentress)	400 mg orally twice daily	Diarrhea, nausea, headache	No special monitoring	\$34.70/400 mg	\$2082.24
Cabotegravir	Oral regimen of 30 mg daily with rilpivirine 25 mg daily for 1 month; then intramuscular loading dose of 600 mg with rilpivirine 900 mg intramuscularly in separate buttock injections; followed by monthly intramuscular injections of 400 mg with 600 mg rilpivirine thereafter.	Injection site reactions with intramuscular dose.	No special monitoring		Monthly maintenance regimen \$4752.00
Entry and Fusion Inhibitors					
Enfuvirtide (Fuzeon)	90 mg subcutaneously twice daily	Injection site pain and allergic reaction	No special monitoring	\$71.71/90 mg	\$4302.67
Maraviroc (Selzentry)	150 mg orally twice daily or 300 mg orally twice daily	Cough, fever, rash	No special monitoring	\$31.12 (for either dose)	\$1867.44 (for either dose)

(continued)

Table 31–7. Antiretroviral therapy agents by class (alphabetical order within class). (continued)

Medication	Dose	Common Side Effects	Special Monitoring ¹	Cost ²	Cost/Month
Entry and Fusion Inhibitors (cont.)					
Ibalizumab (Trogarzo)	Loading dose of 2000 mg intravenously over 30 minutes; maintenance dose of 800 mg intravenously every 2 weeks thereafter	Diarrhea, dizziness, nausea, rash, elevated creatinine, lymphopenia	Monthly CBC, creatinine, bilirubin, glucose, lipase	\$3058.80/400 mg	\$12,235.20
Attachment Inhibitor					
Fostemsavir	600 mg orally twice a day	Nausea	No special monitoring	\$153.00/600 mg	\$9180.00

¹Standard monitoring is complete blood count (CBC) and differential, basic chemistries, serum aminotransferases, and total bilirubin every 3–6 months, urinalysis at baseline and annually during antiretroviral treatment, fasting glucose or hemoglobin A_{1c} at baseline and annually during antiretroviral treatment, and fasting lipid profile at baseline, 4–8 weeks after starting an antiretroviral treatment regimen that affects lipids, and annually for everyone over 40 years of age.

²Average wholesale price (AWP, for AB-rated generic when available) for quantity listed. Source: IBM Micromedex Red Book (electronic version) IBM Watson Health, Greenwood Village, CO, USA. Available at <https://www.micromedexsolutions.com> (cited April 18, 2021). AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions.

to the three-drug rule have emerged. A combination of dolutegravir plus lamivudine (Dovato, Table 31–8) has been shown to be noninferior to dolutegravir plus TDF and emtricitabine as initial therapy in patients with HIV viral load of less than 500,000 copies/mL. A second exception is the coformulation of dolutegravir and rilpivirine (Juluca, Table 31–8); this combination is FDA approved as an alternative treatment for patients who have been successfully virally suppressed for at least 6 months, have no history of treatment failure, and are not resistant to either of the two component agents. A third exception is cabotegravir with rilpivirine as a once-monthly intramuscular injection.

The presence of an acute opportunistic infection in most cases does not preclude the initiation of antiretroviral treatment. Randomized trials compared early initiation of antiretroviral treatment (within 2 weeks of starting treatment for an opportunistic infection or tuberculosis) with antiretroviral treatment that was deferred until after treatment of the opportunistic infection was completed (6 weeks after its start); results demonstrated that early initiation reduced death or AIDS progression by 50%. The reduced progression rates were related to more rapid improvements in CD4 counts in patients with advanced immunodeficiency. Furthermore, IRIS and other adverse events were no more frequent in the early antiretroviral treatment arm.

Several randomized studies have also demonstrated improved clinical outcomes in HIV/tuberculosis coinfecting patients who initiate antiretroviral treatment early in the setting of active treatment for tuberculosis and whose CD4 counts are less than 50 cells/mcL. The exception to early antiretroviral treatment in the setting of active infections may be in patients with a CNS-associated infection, such as cryptococcal or tuberculosis meningitis. Several studies from low-income countries have shown high mortality rates with early antiretroviral treatment initiation in this setting.

An initial antiretroviral regimen should be chosen to minimize side effects. For hospitalized patients, initiating treatment in patients with opportunistic infections requires

close coordination between inpatient and outpatient clinicians to ensure that treatment is continued once patients are discharged.

D. Choosing an Antiretroviral Treatment Regimen

Although the ideal combination of medications has not yet been defined for all possible clinical situations, optimal regimens can be better understood after a review of the available agents. These medications can be grouped into six major categories: nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs); nonnucleoside reverse transcriptase inhibitors (NNRTIs); protease inhibitors (PI); integrase inhibitors; entry and fusion inhibitors; and attachment inhibitors.

1. Nucleoside and nucleotide reverse transcriptase inhibitors (NRTI)—There are currently eight NRTI agents available (counting TDF and TAF as separate agents) for use. The choice of which agent to use depends primarily on the patient's prior treatment experience, results of resistance testing, medication side effects, other underlying conditions, and convenience of formulation. However, most clinicians use fixed-dose combinations (see Table 31–8) of either emtricitabine/TDF, emtricitabine/TAF, or abacavir/lamivudine (ABC/lamivudine), all of which can be given once a day. Abacavir should be given only to HLA-B*5701-negative persons. In patients with viral loads greater than 100,000 copies/mL, ABC/lamivudine was less effective than emtricitabine/TDF when combined with efavirenz or ritonavir-boosted atazanavir. However, ABC/lamivudine appears to be equally efficacious as emtricitabine/TDF in patients with viral loads greater than 100,000 copies/mL when combined with dolutegravir or raltegravir. In some studies, abacavir increased risks of myocardial infarction, and therefore should be avoided in patients at high risk for cardiovascular disease. Zidovudine/lamivudine (AZT/lamivudine) is usually reserved for second- or third-line regimens because of toxicity and dosing schedule. Of the

Table 31–8. Fixed-dose antiretroviral combinations (alphabetical order by brand name).

Name	Components	Dosing and Special Considerations	Cost per Month
Atripla	TDF 300 mg Emtricitabine 200 mg Efavirenz 600 mg	One pill daily constitutes a complete antiretroviral treatment regimen.	\$1920.00
Biktarvy	Emtricitabine 200 mg TAF 25 mg Bictegravir 50 mg	One pill daily constitutes a complete antiretroviral treatment regimen. One of the recommended initial treatment regimens.	\$4072.50
Complera	TDF 300 mg Emtricitabine 200 mg Rilpivirine 25 mg	One pill daily constitutes a complete antiretroviral treatment regimen. Only for patients with HIV viral load < 100,000/mL.	\$3706.28
Delstrigo	TDF 300 mg Lamivudine 300 mg Doravirine 100 mg	One pill daily constitutes a complete antiretroviral treatment regimen.	\$2778.12
Descovy	TAF 25 mg Emtricitabine 200 mg	One pill daily along with an NNRTI, protease inhibitor, integrase inhibitor, or maraviroc (entry inhibitor). The difference between Descovy and Truvada is that Descovy has a different form of tenofovir (TAF) that appears to have less effect on kidney function and bone mineral density than the form of tenofovir (TDF) in Truvada. Descovy is approved for use as a single agent for PrEP in men (not studied in women).	\$2316.85
Dovato	Dolutegravir 50 mg Lamivudine 300 mg	One pill daily constitutes a complete antiretroviral treatment regimen in adults with no prior antiviral treatment and no known substitutions associated with resistance to either component.	\$3032.81
Epzicom	Abacavir 600 mg Lamivudine 300 mg	One pill daily along with an NNRTI, protease inhibitor, integrase inhibitor, or maraviroc (entry inhibitor).	\$1393.50
Genvoya	TAF 10 mg Emtricitabine 200 mg Elvitegravir 150 mg Cobicistat 150 mg	One pill daily constitutes a complete antiretroviral treatment regimen. Although it contains four medications, one component (cobicistat) is a medication booster only. The only difference between Stribild and Genvoya is that Genvoya has a different form of tenofovir (TAF) that appears to be safer than tenofovir TDF with less effect on kidney function and bone mineral density.	\$4072.50
Juluca	Dolutegravir 50 mg Rilpivirine 25 mg	One pill daily with a meal for patients who have been virologically suppressed (viral load < 50 copies/mL) on a stable antiretroviral treatment regimen for ≥ 6 months and no history of treatment failure or resistance to dolutegravir or rilpivirine.	\$3578.52
Odefsey	TAF 25 mg Emtricitabine 200 mg Rilpivirine 25 mg	One pill daily constitutes a complete antiretroviral treatment regimen. Only for patients with no history of HIV viral load ≥ 100,000 copies/mL. Or for replacement of stable antiretroviral regimen in patients fully suppressed for > 6 months, with no history of treatment failure, and with no known resistance to components of the drug combination.	\$3706.28
Stribild	TDF 300 mg Emtricitabine 200 mg Elvitegravir 150 mg Cobicistat 150 mg	One pill daily constitutes a complete antiretroviral treatment regimen. Although it contains four medications, one component (cobicistat) is a medication booster only.	\$4272.06
Syntuzta	TAF 10 mg Emtricitabine 200 mg Darunavir 800 mg Cobicistat 150 mg	One pill daily constitutes a complete antiretroviral treatment regimen. Although it contains four medications, one component (cobicistat) is a medication booster only. One of the recommended initial treatment regimens.	\$4877.76
Triumeq	Abacavir 600 mg Lamivudine 300 mg Dolutegravir 50 mg	One pill constitutes a complete antiretroviral treatment regimen. One of the recommended initial treatment regimens.	\$3818.26
Trizivir	Abacavir 300 mg Lamivudine 150 mg Zidovudine 300 mg	One tablet twice daily with an NNRTI, protease inhibitor, integrase inhibitor, or maraviroc (entry inhibitor). Although it contains three medications it does not constitute a complete antiretroviral treatment regimen.	\$1738.46
Truvada	TDF 300 mg Emtricitabine 200 mg	One pill daily with an NNRTI, protease inhibitor, integrase inhibitor, or maraviroc (entry inhibitor). TDF is the most commonly used NRTI backbone. Truvada is approved for use as a single agent for PrEP.	\$2100.20

NNRTI, non-nucleoside reverse transcriptase inhibitor (eg, delavirdine, efavirenz, etravirine, nevirapine, rilpivirine); NRTI, nucleoside/nucleotide reverse transcriptase inhibitor (eg, abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zidovudine); PrEP, preexposure prophylaxis; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Average wholesale price (AWP, for AB-rated generic when available) for quantity listed. Source: IBM Micromedex Red Book (electronic version) IBM Watson Health, Greenwood Village, CO, USA. Available at <https://www.micromedexsolutions.com> (cited April 18, 2021). AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions.

available agents, zidovudine is the most likely to cause anemia. Zidovudine and didanosine are the most likely to cause neutropenia. Stavudine is the most likely to cause lipoatrophy (loss of fat in the face, extremities, and buttocks) and should no longer be used; zidovudine is the next most likely agent to cause lipoatrophy. Didanosine is the most likely to cause peripheral neuropathy. Emtricitabine, TDF, TAF, and lamivudine have activity against hepatitis B. Didanosine, emtricitabine, TDF, TAF, and lamivudine can be administered once daily. Information specific to each medication is given below and in Table 31–7.

A. ZIDOVUDINE—Zidovudine was the first approved antiviral medication for HIV infection. It is administered at a dose of 300 mg orally twice daily. A combination of zidovudine 300 mg and lamivudine 150 mg (Combivir) is available. Approximately 40% of patients experience subjective side effects that usually remit within 6 weeks. The common dose-limiting side effects are anemia and neutropenia, which require ongoing laboratory monitoring. Long-term use has been associated with lipoatrophy.

B. LAMIVUDINE—Lamivudine is a safe and well-tolerated agent. The dosage is 150 mg orally twice daily or 300 mg orally once a day. The dose should be reduced in patients with chronic kidney disease. There are no significant side effects with lamivudine; it has activity against hepatitis B, though HBV resistance to it is an increasing problem.

C. EMTRICITABINE—Emtricitabine is dosed at 200 mg orally once daily. Emtricitabine also has activity against hepatitis B. Its dosage should be reduced in patients with chronic kidney disease.

D. ABACAVIR—Abacavir is dosed at 300 mg orally twice daily. Prior to initiation of abacavir, patients should undergo testing for HLA typing. Those with the B*5701 allele should not be treated with abacavir because the likelihood of a hypersensitivity reaction developing is high; the reaction is characterized by a flu-like syndrome with rash and fever that worsens with successive doses. Unfortunately, the absence of this allele does not guarantee that the patient will avoid the hypersensitivity reaction. Individuals in whom the hypersensitivity reaction develops *should not* be rechallenged with this agent because subsequent hypersensitivity reactions can be fatal. Abacavir has also been associated with an increased risk of myocardial infarction in some cohort studies, generally in patients who have underlying risks for cardiovascular disease. Consequently, abacavir should not be used in such patients if effective alternative nucleoside or nucleotide analog agents exist. Abacavir is usually prescribed as a fixed-dose combination pill with lamivudine for use as a once-daily pill (Epzicom; Table 31–8).

Abacavir is also formulated with zidovudine and lamivudine in a single pill (Trizivir, one tablet orally twice daily; Table 31–8). Trizivir is not recommended as solo treatment for HIV because it is not as efficacious as combining two nucleoside/nucleotide analogs with a ritonavir-boosted PI, an NNRTI, or an integrase inhibitor.

E. TENOFOVIR—Tenofovir is the only licensed nucleotide analog. It comes in two forms: tenofovir disoproxil

fumarate (TDF) and tenofovir alafenamide (TAF). TDF is available for use both in the form of a single pill at an oral dose of 300 mg once daily and as an oral fixed-dose combination pill with emtricitabine 200 mg (Truvada; Table 31–8) once daily. Several other single-tablet once-a-day complete regimens include TDF (Atripla, Complera, Stribild) (Table 31–8). Tenofovir is active against hepatitis B, including isolates that have resistance to lamivudine. TDF is associated with a clinically modest loss of kidney function, a small increased risk of acute kidney injury, and increased rate of bone resorption. In patients taking boosted therapy (eg, therapy including cobicistat or ritonavir), TAF appears to cause fewer problems with kidney dysfunction and bone loss and is the preferred choice.

TAF attains higher levels in cells with a much lower plasma level. For this reason, it appears to cause less harm to kidneys and less bone resorption. TAF should not be used with rifamycins. TDF appears to be associated with lower lipid levels, and TAF seems to be associated with greater weight gain when combined with integrase inhibitors.

If tenofovir (both TDF and TAF) cannot be avoided in patients with creatinine clearance below 60 mL/min, their kidney function should be monitored very closely. It is recommended that the serum creatinine be checked at baseline, at 2–8 weeks, and then every 3–6 months and that a urinalysis and urine glucose and protein be checked at baseline and monitored periodically as clinically indicated.

F. DIDANOSINE—The most convenient formulation of didanosine is the enteric-coated capsule. For adults weighing at least 60 kg, the dose is one 400-mg enteric-coated capsule orally daily; for those 30–59 kg, the dose is one 250-mg enteric-coated capsule orally daily. Didanosine should be taken on an empty stomach.

Didanosine has been associated with pancreatitis. The incidence of pancreatitis with didanosine is 5–10%—of fatal pancreatitis, less than 0.4%. Patients with a history of pancreatitis, as well as those taking other medications associated with pancreatitis (including trimethoprim-sulfamethoxazole and intravenous pentamidine) are at higher risk for this complication. Other common side effects with didanosine include a dose-related, reversible, painful peripheral neuropathy, which occurs in about 15% of patients, and dry mouth. Fulminant hepatic failure and electrolyte abnormalities, including hypokalemia, hypocalcemia, and hypomagnesemia, have been reported in patients taking didanosine. Because of the side-effect profile, didanosine is rarely used today.

2. Nonnucleoside reverse transcriptase inhibitors—NNRTIs inhibit reverse transcriptase at a site different from that of the nucleoside and nucleotide agents described above. The major advantage of NNRTIs is that four of them (efavirenz, rilpivirine, doravirine, and nevirapine) have potencies comparable to that of PI (next section), at least for patients with viral loads under 100,000 copies/mL—with lower pill burden and fewer side effects. Unlike PI, they do not appear to cause lipodystrophy; patients with cholesterol and triglyceride elevations who are switched from a PI to an NNRTI may have improvement in their

lipids. The resistance patterns of NNRTIs are distinct from those of the PIs. Because these agents may cause alterations in the clearance of PIs, dose modifications may be necessary when these two classes of medications are administered concomitantly. There is a high degree of cross-resistance among the “first-generation” NNRTIs, such that resistance to one medication in this class uniformly predicts resistance to other medications. However, the “second-generation” NNRTI etravirine appears to have consistent antiviral activity in patients with prior exposure and resistance to nevirapine, efavirenz, or delavirdine. In particular, the *K103N* mutation does not appear to have an impact on etravirine (or rilpivirine). There is no therapeutic reason for using more than one NNRTI at the same time.

A. EFAVIRENZ—The major advantages of efavirenz are that it can be given once daily in a single dose (600 mg orally) and it is available in a once-daily fixed-dose combination with TDF and emtricitabine in a single pill (Atripla; Table 31–8). The major side effects are rash and psychiatric/neurologic complaints, with patients reporting symptoms ranging from lack of concentration and strange dreams to delusions and mania. These side effects tend to wane over time, usually within a month or so; however, there are some patients who cannot tolerate these effects, especially if they persist longer than a month. Participant level data from four randomized trials of efavirenz regimens versus non-efavirenz containing regimens found increased suicidality (hazard ratio of 2.6) among those taking efavirenz. Administration of efavirenz with food, especially fatty food, may increase its serum levels and consequent neurotoxicity. Therefore, it should be taken on an empty stomach; taking before bedtime may also reduce patients’ experience of neuropsychiatric symptoms.

B. DORAVIRINE—Dosed at 100 mg orally daily, this drug can be taken with or without food. Two 48-week phase 3 studies showed that, in previously untreated individuals, doravirine, when used with two NRTIs resulted in similar levels of viral suppression as efavirenz plus two NRTIs or darunavir/ritonavir plus two NRTIs. It is also available as a single-pill combination with TDF and lamivudine (Delstrigo; Table 31–8). It is well tolerated. In cases of virologic failure, NNRTI cross-resistance may develop.

C. RILPIVIRINE—This medication, dosed at 25 mg once daily, is equal in efficacy to efavirenz in patients with HIV viral loads below 100,000 copies/mL. Rilpivirine should not be used in patients with baseline viral loads of 100,000 copies/mL or greater or those with CD4 counts below 200 cells/mcL because of greater risk of viral failure. As is true of efavirenz, rilpivirine is available in a once-daily fixed-dose combination with TDF and emtricitabine (Complera; Table 31–8) and with TAF and emtricitabine (Odefsey; Table 31–8) to be taken with a meal. It is also available in a two-drug regimen with dolutegravir (Juluca; Table 31–8). Proton pump inhibitors should not be given with rilpivirine. Rilpivirine has fewer neurologic side effects than efavirenz. The FDA has approved a long-acting formulation of rilpivirine for monthly intramuscular injections to be given with the integrase inhibitor cabotegravir (see below).

D. NEVIRAPINE—The dose of nevirapine is 400 mg orally daily (extended release), but it is initiated at a dose of 200 mg once a day to decrease the incidence of rash, which is as high as 40% when full doses are begun immediately. If rash develops while the patient is taking 200 mg daily, liver enzymes should be checked and the dose should not be increased until the rash resolves. Patients with mild rash and no evidence of hepatotoxicity can continue to be treated with nevirapine. Nevirapine should not be used in treatment-naïve women with CD4 counts greater than 250 cells/mcL or in males with CD4 counts greater than 400 cells/mcL because they have greater risk of hepatotoxicity. In general, because of the risk of fatal hepatotoxicity, nevirapine should be used only when there is not a better alternative.

E. DELAVIRDINE—Of the available NNRTIs, delavirdine is used the least largely because of its inconvenient dosing and pill burden compared with the other available NNRTIs. Unlike nevirapine and efavirenz, delavirdine inhibits P450 cytochromes rather than inducing these enzymes. This means that delavirdine can act like ritonavir and boost other antiretrovirals, although delavirdine is not as potent as ritonavir in this capacity. The dosage is 400 mg orally three times a day. The major side effect is rash.

F. ETRAVIRINE—Etravirine is an NNRTI approved for the treatment of patients with prior NNRTI intolerance or resistance. Etravirine has been shown to be effective even when some degree of NNRTI resistance is present, making it a true “second-generation” medication in this class. Etravirine dosage is one 200-mg tablet twice daily. It should be used with a PI and an NRTI and not just with two NRTIs. The most common side effects are nausea and rash; rarely, the rash can be severe (toxic epidermal necrolysis). Patients with signs of severe rash or hypersensitivity reactions should immediately discontinue the medication. Prior rash due to treatment with one of the other NNRTIs does not make rash more likely with etravirine. Etravirine should not be taken by people with severe liver disease or administered with tipranavir/ritonavir, fosamprenavir/ritonavir, atazanavir/ritonavir, full-dose ritonavir, or PI without low-dose ritonavir.

3. Protease inhibitors—Ten PIs—indinavir, nelfinavir, ritonavir, saquinavir, amprenavir, fosamprenavir, lopinavir (in combination with ritonavir), atazanavir, darunavir, and tipranavir—are available. PIs are potent suppressors of HIV replication and are administered as part of a combination regimen.

All of the PIs—to differing degrees—are metabolized by the cytochrome P450 system, and each can inhibit and induce various P450 isoenzymes. Therefore, medication interactions are common and difficult to predict. Clinicians should consult the product inserts before prescribing PIs with other medications. Medications such as rifampin that are known to induce the P450 system should be avoided.

The fact that the PIs are dependent on metabolism through the cytochrome P450 system has led to the use of ritonavir to boost the medication levels of saquinavir, lopinavir, indinavir, atazanavir, tipranavir, darunavir, and

amprenavir, allowing use of lower doses and simpler dosing schedules of these PIs. A second boosting agent, cobicistat, is coformulated with the PI atazanavir (Evotaz) and darunavir (Prescovix). Similar to ritonavir, cobicistat also inhibits liver enzymes that metabolize other HIV medications.

In fact, guidelines recommend that all PI-containing regimens except nelfinavir use boosting if possible.

When choosing which PI to use, prior patient experience, resistance patterns, side effects, and ease of administration are the major considerations. The first three PIs to be developed—indinavir, saquinavir, and ritonavir (as single agents)—are now rarely used because of the superiority of the second generation of PIs. Amprenavir has been almost entirely replaced by its prodrug, fosamprenavir. Unfortunately, all PIs, with the exception of unboosted atazanavir have been linked to a constellation of metabolic abnormalities, including elevated cholesterol levels, elevated triglyceride levels, insulin resistance, diabetes mellitus, and changes in body fat composition (eg, buffalo hump, abdominal obesity). The lipid abnormalities and body habitus changes are referred to as **lipodystrophy**. Although lipodystrophy is commonly associated with PIs, it has been seen also in HIV-infected persons who have never been treated with these agents. In particular, the lipoatrophy effects seen in patients receiving antiretroviral treatment appears to be more related to the nucleoside toxicity and in particular to the thymidine analogs (stavudine and zidovudine).

Of the different manifestations of lipodystrophy, the dyslipidemias that occur are of particular concern because of the likelihood that increased levels of cholesterol and triglycerides will result in increased prevalence of heart disease. All patients taking PIs or NRTIs should have fasting serum cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels performed every 12 months. Clinicians should assess for coronary heart disease risk (see Chapter 28) and consider initiating dietary changes or medication therapy (or both). PIs inhibit statin metabolism. Lovastatin and simvastatin should be avoided. In general, the least interaction is with pravastatin (20 mg daily orally). Atorvastatin (10 mg daily orally) or rosuvastatin (5 mg/day orally initially; maximum 10 mg/day) may also be used cautiously. Fish oil (3000 mg daily) combined with exercise and dietary counseling has been found to decrease triglyceride levels by 25%. Patients with persistently elevated fasting serum triglyceride levels of 500 mg/dL or more who do not respond to dietary intervention should be treated with gemfibrozil (600 mg twice daily prior to the morning and evening meals). PIs are associated with abnormalities in cardiac conduction, especially prolongation of the PR interval.

A. INDINAVIR—Indinavir is usually dosed at 800 mg twice daily in combination with 100 mg of ritonavir twice daily. Nausea and headache are common complaints with this medication. Indinavir crystals are present in the urine in approximately 40% of patients; this results in clinically apparent nephrolithiasis in about 15% of patients receiving indinavir. Lower urinary tract symptoms and acute kidney injury also have been reported. Patients taking this medication should be instructed to drink at least 48 ounces of fluid a day to ensure adequate hydration in an attempt to limit

these complications. Mild indirect hyperbilirubinemia is also commonly observed in patients taking indinavir but is not an indication for discontinuation of the medication.

B. SAQUINAVIR—Saquinavir is formulated only as a hard-gel capsule (Invirase). It should be used only with ritonavir (1000 mg of hard-gel saquinavir with 100 mg of ritonavir orally twice daily). The most common side effects with saquinavir are diarrhea, nausea, dyspepsia, and abdominal pain.

C. RITONAVIR—Use of this potent PI at full dose (600 mg orally twice daily) has been limited by its inhibition of the cytochrome P450 pathway causing a large number of drug-drug interactions and by its frequent side effects of fatigue, nausea, and paresthesias. However, it is widely used in lower dose (eg, 100 mg daily to 100 mg twice daily) as a booster of other PIs.

D. NELFINAVIR—Nelfinavir is the only PI for which ritonavir boosting is not recommended. Unboosted nelfinavir is generally not as potent as a boosted PI regimen (eg, lopinavir plus ritonavir). The dose of nelfinavir is 1250 mg orally twice daily. Diarrhea is a side effect in 25% of patients taking nelfinavir, but this symptom may be controlled with over-the-counter antidiarrheal agents in most patients.

E. AMPRENAVIR—Amprenavir has efficacy and side effects similar to those of other PIs. Common side effects are nausea, vomiting, diarrhea, rash, and perioral paresthesia. The dose is 1200 mg orally twice daily. The concentration of amprenavir decreases when coadministered with ethinyl estradiol; therefore, amprenavir should be used with circumspection in the treatment of transgender persons requiring high-dose estrogen.

F. FOSAMPRENAVIR—Fosamprenavir is a prodrug of amprenavir. Its major advantage over using amprenavir is a much lower pill burden. For PI-naïve patients, it can be dosed at 1400 mg orally twice daily (four capsules a day) or at 1400 mg orally daily (two capsules) with ritonavir 200 mg orally daily (two capsules) or at 700 mg orally with ritonavir 100 mg orally twice daily. Patients previously treated with a PI should receive 700 mg orally with ritonavir 100 mg orally twice daily. Side effects are similar to those with amprenavir—most commonly gastrointestinal distress and hyperlipidemia. As with amprenavir, the concentration of fosamprenavir decreases when coadministered with ethinyl estradiol; therefore, fosamprenavir should be used with circumspection in the treatment of transgender persons requiring high-dose estrogen.

G. LOPINAVIR/R—Lopinavir/r is lopinavir (200 mg) coformulated with a low dose of ritonavir (50 mg) to maximize the bioavailability of lopinavir. It has been shown to be more effective than nelfinavir when used in combination with stavudine and lamivudine. The usual dose is lopinavir 400 mg with ritonavir 100 mg (two tablets) orally twice daily with food. When given along with efavirenz or nevirapine, a higher dose (600 mg/150 mg—three tablets) is usually prescribed. The most common side effect is diarrhea, and lipid abnormalities are frequent. Because of these side effects, lopinavir/r has fallen off the list of medications recommended as part of first-line treatment regimens.

H. ATAZANAVIR—Atazanavir is available alone and coformulated with cobicistat (Evotaz). Atazanavir can be dosed as 400 mg (two 200-mg capsules) daily with food or it can be dosed as 300 mg in combination with 100 mg of ritonavir once daily with food. When coformulated with cobicistat, it is dosed at 300-mg atazanavir and 150-mg cobicistat. The most common side effect is mild hyperbilirubinemia that resolves with discontinuation of the medication. Nephrolithiasis and cholelithiasis have also been reported with this PI. Both tenofovir and efavirenz lower the serum concentration of atazanavir. Therefore, when either of these two medications is used with atazanavir, it should be boosted by administering ritonavir or given coformulated with cobicistat. Proton pump inhibitors are contraindicated in patients taking atazanavir because atazanavir requires an acidic pH to remain in solution.

I. TIPRANAVIR—Tipranavir is the only nonpeptidic PI approved by the FDA. Because of its unique structure, it is active against some strains of HIV that are resistant to other PIs. It is dosed with ritonavir (two 250-mg capsules of tipranavir with two 100-mg capsules of ritonavir orally twice daily with food). The most common side effects are nausea, vomiting, diarrhea, fatigue, and headache. Tipranavir/ritonavir has been also associated with liver damage and should be used very cautiously in patients with underlying liver disease. Reports of intracranial hemorrhage in patients taking tipranavir-containing regimens have raised additional safety concerns about this potent PI. Because it is a sulfa-containing medication, its use should be closely monitored in patients with sulfa allergy.

J. DARUNAVIR—Darunavir has impressive antiviral activity in the setting of significant PI resistance and in treatment-naïve patients. It is formulated by itself and coformulated with cobicistat (Prezcobix). When formulated without cobicistat it requires boosting with ritonavir. For initial treatment of HIV or for treatment-experienced patients without darunavir-related resistance mutations, daily dosing is 800 mg of darunavir with 100 mg of ritonavir or with 150 mg of cobicistat. Darunavir 800 mg is also available in a coformulated tablet with emtricitabine, TAF, and cobicistat (Symtuza, Table 31–8). It has been approved for use by the FDA and the European Commission. For patients with prior PI treatment experience or PI resistance (with mutations known to impact darunavir), darunavir should be dosed at 600 mg orally twice daily, with ritonavir, 100 mg orally twice daily. Darunavir has a safety profile similar to other PIs, such as ritonavir-boosted lopinavir, but is generally better tolerated. Like tipranavir, darunavir is a sulfa-containing medication, and its use should be closely monitored in patients with sulfa allergy.

4. Integrase inhibitors—Integrase inhibitors slow HIV replication by blocking the HIV integrase enzyme needed for the virus to multiply. They are now the preferred regimens for initiating therapy because of the combination of efficacy, ease of administration, and low incidence of side effects. Five integrase inhibitors are currently available: raltegravir; elvitegravir; dolutegravir; bictegravir; and cabotegravir, which is to be given by monthly injections along with monthly injections of rilpivirine. Clinical trials of available

integrase inhibitors reveal a consistent pattern of more rapid decline in viral load compared with more standard PI/r or NNRTI-based regimens. Integrase inhibitors are effective (when combined with other active medications) in the treatment of HIV-infected patients with documented resistance to each of the three main classes of antiretroviral medications (nucleoside analogs, PIs, NNRTIs). Avoid administering oral integrase inhibitors with antacids or other medications with divalent cations (Ca^{2+} , Mg^{2+} , Al^{2+} , Fe^{2+}) because chelation of the integrase inhibitor by the cation reduces absorption. When these medications must be taken with integrase inhibitors, consult a pharmacist to determine the best separation of times of administration.

A. RALTEGRAVIR—The dose of raltegravir is 400 mg orally twice daily. It has been found to be superior to efavirenz and ritonavir-boosted darunavir and ritonavir-boosted atazanavir. It is the recommended integrase inhibitor for pregnant women. Common side effects are diarrhea, nausea, and headache, but overall, it is well tolerated and has the additional advantage over PI-based regimens and efavirenz-based regimens in that it appears to have little impact on lipid profiles or glucose metabolism.

B. ELVITEGRAVIR—Elvitegravir is not manufactured as a single agent. It can be prescribed in a once-a-day combination pill (Stribild) that contains 125 mg of elvitegravir and 150 mg of cobicistat, a boosting agent, along with standard doses of TDF and emtricitabine (Table 31–8). Stribild has been shown to be noninferior to two preferred first-line regimens: Atripla and boosted atazanavir with emtricitabine/TDF. The main side effect of Stribild is an increase in serum creatinine levels that has been shown to be related to the cobicistat inhibition of tubular secretion of creatinine by the kidney and is thought to be nonpathologic and reversible. However, because of this effect, Stribild is recommended in patients with estimated creatinine clearance greater than 70 mL/min. A urinalysis should be done at baseline and at initial follow-up to look for proteinuria and glycosuria, which are signs of tubulopathy. Diarrhea and rash may also occur, although overall the medication is well tolerated. Elvitegravir is also coformulated with emtricitabine and TAF along with cobicistat boosting in a single once-a-day pill (Genvoya, Table 31–8). Since TAF appears to have fewer side effects than TDF, this is likely to become the preferred elvitegravir regimen.

C. DOLUTEGRAVIR—Dolutegravir shows excellent potency and tolerability and is dosed once a day in most circumstances. It has been shown to be superior to efavirenz and darunavir. Unlike elvitegravir, dolutegravir does not require a boosting agent and has fewer drug-drug interactions. Similar to cobicistat, it inhibits tubular secretion of creatinine by the kidney, resulting in small increases in serum creatinine levels. The standard dosage used in treatment-naïve, integrase-naïve patients is 50 mg/day. It is available combined with abacavir and lamivudine in a single once a day tablet (Triumeq, Table 31–8). In patients receiving efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin, the dose should be increased to 50 mg twice daily. It should also be dosed at 50 mg twice daily in integrase-experienced patients in whom integrase

resistance is suspected. Indeed, when combined with other active medications, it has been shown to provide some activity in patients with integrase resistance who have not responded to prior raltegravir- or elvitegravir-containing regimens. Dolutegravir has demonstrated impressive results in clinical trials of treatment-naïve patients, in terms of effectiveness, tolerability, and high barrier to resistance, when compared with the more standard NNRTI, boosted PI, and raltegravir-containing regimens. Dolutegravir is coformulated in combination with rilpivirine (Juluca, Table 31–8) for use as a once-a-day (to be taken with a meal) treatment for patients who are virologically suppressed (viral load less than 50 copies/mL) on a stable regimen for at least 6 months, with no history of treatment failures or resistance to either of the two agents.

D. BICTEGRAVIR—Bictegravir is dosed once daily, does not require boosting, and has a high barrier to resistance. It is dosed at 50 mg daily. It has been shown to be noninferior to dolutegravir. It is not available as a single agent but is marketed as a fixed-dose combination of bictegravir with emtricitabine and TAF (Biktarvy, Table 31–8).

E. CABOTEGRAVIR—Cabotegravir is an integrase inhibitor that has been approved for use in the United States, Canada, and in the European Union. Cabotegravir comes in two forms: an oral tablet and an injectable formulation. In both forms, it is intended to be given with rilpivirine. The oral form is meant only for the first month of therapy to ensure that the patient is able to tolerate the medication before injecting it in its long-acting formulation. Oral dosing is 30 mg daily of cabotegravir with 25 mg daily of rilpivirine. When given intramuscularly in combination with rilpivirine, the cabotegravir and rilpivirine are given as separate injections at the same time, one in each buttock. The first intramuscular loading doses are cabotegravir 600 mg and rilpivirine 900 mg. Thereafter, monthly intramuscular dosing is 400 mg of cabotegravir and 600 mg of rilpivirine. The advantage of this combination is that it is complete therapy for patients in whom the viral load is stable and suppressed (less than 50 copies) on their current regimen, which is then stopped in favor of cabotegravir/rilpivirine. The most common side effect is injection site reactions.

5. Entry and fusion inhibitors—

A. ENFUVIRTIDE—Enfuvirtide (Fuzeon) is known as a fusion inhibitor; it blocks the entry of HIV into cells by blocking the fusion of the HIV envelope to the cell membrane. The addition of enfuvirtide to an optimized antiretroviral regimen improved CD4 counts and lowered viral loads in heavily pretreated patients with multidrug-resistant HIV. Unfortunately, resistance to enfuvirtide develops rapidly in patients receiving a nonsuppressive treatment regimen. The dose is 90 mg by subcutaneous injection twice daily; unfortunately, painful injection site reactions develop in most patients, which makes long-term use problematic.

B. MARAVIROC—Maraviroc is a CCR5 co-receptor antagonist. Medications in this class prevent the virus from entering uninfected cells by blocking the CCR5 co-receptor. Before starting therapy, a viral tropism assay should be

performed because this class of entry inhibitors is only active against “CCR5-tropic virus.” This form of the HIV-1 virus tends to predominate early in infection, while so-called dual/mixed tropic virus (which utilizes either R5 or CXCR4 co-receptors) emerges later as infection progresses. Approximately 50–60% of previously treated HIV-infected patients have circulating CCR5-tropic HIV. The medication has been shown to be effective in HIV-infected persons who have CCR5-tropic virus and ongoing viral replication despite being heavily treated. The dose of maraviroc is 150–300 mg orally twice daily, based on the other medications the patient is taking at the time—in combination with a ritonavir boosted PI, 150 mg daily of maraviroc has been used successfully. Common side effects are cough, fever, rash, musculoskeletal problems, abdominal pain, and dizziness; however, maraviroc is generally well tolerated with limited impact on serum lipids.

C. IBALIZUMAB—A novel treatment for HIV, ibalizumab is a monoclonal antibody that blocks the entry of HIV into the CD4 cell by blocking the CD4 receptor. Given as an intravenous infusion therapy along with other oral HIV medications, it is used as rescue therapy for patients with multidrug-resistant HIV that is not controlled by other treatments. It is given every 2 weeks. Common side effects include diarrhea, dizziness, nausea, rash, elevations in creatinine, and lymphopenia.

6. Attachment inhibitor—

FOSTEMAVIR—The active metabolite of fostemavir, temsavir, binds to the viral envelope glycoprotein 120, near to the CD4 binding site, such that the virus does not attach to the CD4 cells and cannot enter them. With its unique mechanism, it has no cross resistance with other antiretrovirals. Unlike maraviroc, it is effective regardless of HIV-1 tropism. It is FDA approved for use in heavily treatment-experienced adults with multidrug-resistant HIV-1 infection who are not responding to their current regimen. The dosage of fostemavir is 600 mg orally twice daily, along with an optimized regimen of other antiretroviral medications. It should not be used in conjunction with drugs that are strong P450 (CYP)3A inducers, such as rifampin, phenytoin, and St John’s wort.

7. Constructing an initial regimen—Guidelines for starting antiretroviral treatment are shown in Table 31–9. The regimens with the strongest evidence all contain integrase inhibitors. This reflects their high efficacy, high barrier to resistance, tolerability, low pill burden, and safety profile. The two easiest integrase inhibitors to use are bictegravir and dolutegravir and so they form the backbone of the recommended regimens. With respect to nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs), the safest, most effective, easiest to use are TDF and TAF and then emtricitabine or lamivudine. From an efficacy standpoint, there is no difference between TDF or TAF; for patients on a boosted regimen (ie, one including cobicistat or ritonavir), those with renal dysfunction or osteoporosis or osteopenia (or risk for these conditions) should receive TAF. Also, choosing between TDF and TAF may depend on convenience: which one is coformulated with other desired partner drugs. Emtricitabine and lamivudine are

essentially the same from the point of view of efficacy and side effects.

For the first time, there is a two-drug regimen included in the top recommended regimens: dolutegravir plus lamivudine, which is available as a single pill for once-a-day treatment (Dovato, Table 31–8). (All other recommended regimens contain three drugs, sometimes with a fourth agent as a booster.) This two-drug regimen is not recommended for patients with high HIV viral load (greater than 500,000 copies/mL), or for patients with HBV coinfection (because of development of resistance by the hepatitis B virus to lamivudine when used as monotherapy with possibility of severe flares of hepatitis), or for patients for whom the results from HIV resistance or HBV testing are not yet available. There is also concern about its use in patients with CD4 cell counts less than 200/mL.

Studies have shown dolutegravir/abacavir/lamivudine to be superior to efavirenz/TDF/emtricitabine and have shown dolutegravir to be superior to ritonavir-boosted darunavir (both combined with either abacavir/lamivudine or TDF/emtricitabine). A network meta-analysis adjusting for NRTI backbone found that dolutegravir had superior efficacy in suppressing viral load compared with regimens containing ritonavir-boosted atazanavir, ritonavir-boosted darunavir, efavirenz, or ritonavir-boosted lopinavir. Discontinuation due to adverse events was also statistically lower with the dolutegravir regimens.

The drug combinations incorporating the integrase inhibitor raltegravir have done well in comparative studies. Among treatment-naïve patients, raltegravir in combination with TDF/emtricitabine is as effective as efavirenz/TDF/emtricitabine for daily treatment and has fewer side effects. In a 5-year follow-up to the double-blind trial, the raltegravir arm outperformed the efavirenz combination regimen largely due to better long-term tolerability. Furthermore, the CD4 response appeared better in patients treated with the raltegravir combination.

Neural tube defects are increased in the offspring of women taking dolutegravir at conception, so use in women of reproductive age requires informed consent. The integrase inhibitor raltegravir is recommended for women who are already pregnant. Elvitegravir/cobicistat and other drugs boosted with cobicistat should not be used during pregnancy and neither should bictegravir (because of lack of data regarding adverse effects). Recommended drugs in pregnancy include atazanavir/ritonavir, darunavir/ritonavir, efavirenz, and rilpivirine.

The emergence of generic antiretroviral medications is also likely to affect prescribing choices when equally effective regimens are available at different costs. There are generic versions available for abacavir, atazanavir, efavirenz, lamivudine, and TDF. But how this will affect the costs patients pay can be very difficult to determine because of complicated copay rules.

For patients who cannot take an integrase inhibitor, alternative regimens are recommended (Table 31–9).

Resistance testing should be performed prior to starting antiretroviral treatment. Of newly infected persons in some urban areas of the United States, 8–10% have NNRTI resistance (primarily K103N). Patients with NNRTI resistance

would not be expected to respond fully to an efavirenz-based regimen.

The most important determinant of treatment efficacy is adherence to the regimen. Therefore, it is vitally important that the regimen chosen be one to which the patient can easily adhere (Figure 31–7). In general, patients are more compliant if their medication regimens (Table 31–9) offer complete therapy in one pill that needs to be taken only once or twice a day, do not require special timing with regard to meals, can be taken at the same time as other medications, do not require refrigeration or special preparation, and do not have bothersome side effects. Given the high level of effectiveness of recommended regimens, patients for whom the viral load does not fully suppress are likely noncompliant. Pharmacists and other specially trained clinicians can be very effective in helping patients improve their adherence by taking the time to understand why patients miss their medications and to problem solve (eg, take medicine at same time every day, keep a supply in the car or at work in case they forget). For certain populations (eg, unstably housed individuals), specially tailored programs that include medication dispensing are needed.

E. Monitoring Antiretroviral Treatment

1. Goals of monitoring antiretroviral treatment—Monitoring of antiretroviral treatment (Figure 31–7) has two goals: evaluate for toxicity and measure efficacy using objective markers to determine whether to maintain or change regimens. Laboratory evaluation for toxicity depends on the specific medications in the combination but generally should be done approximately every 3–4 months once a patient is on a stable regimen. Patients who are intolerant of their initial regimen should be changed to one of the other initial recommended or alternative regimens in Table 31–9. The second aspect of monitoring is to measure objective markers of efficacy. The CD4 cell count and HIV viral load should be repeated 1–2 months after the initiation or change of antiretroviral regimen and every 3–6 months thereafter in clinically stable patients. With integrase regimens, approximately 80% of patients will have undetectable HIV viral load at 1 month. All patients should have undetectable viral loads by 3 months; if not, the usual problem is nonadherence (see below). (Patients receiving antiretroviral treatment with undetectable viral load for 2 years and CD4 counts 300 cells/mL or more may need CD4 testing only every 12 months.)

2. The challenge of medication compliance—In a patient who is adherent to an effective regimen, viral loads should be undetectable within 4–12 weeks. For patients in whom viral loads are not suppressed or who have viral rebound after suppression, the major question facing the clinician is whether the patient is nonadherent or has resistance to the regimen, or both. The issue is complicated because many patients report being more compliant than they really are. Patients who are having trouble adhering to their treatment should receive counseling on how to better comply with their treatment. In patients who are adherent or who have missed enough doses to make resistance possible, resistance testing should be performed. Based on the results of

Table 31–9. Recommended and alternative initial antiretroviral therapy (ART) regimens (alphabetical order).

Regimen	Advantages	Disadvantages
Recommended Initial Regimens		
Bictegravir + TAF + emtricitabine (Bictegravir)	Single pill once-a-day regimen Low risk of resistance Noninferior to dolutegravir	Less experience than with dolutegravir
Dolutegravir (50 mg daily) ¹ + Either: emtricitabine/TDF or emtricitabine/TAF or lamivudine/TDF or lamivudine/TAF	Has activity in some patients with integrase resistance Once-a-day regimen Dolutegravir plus either abacavir/lamivudine or emtricitabine/TDF is superior to darunavir/ritonavir plus either of the NRTI backbones	Dolutegravir has an increased risk of infant neural tube defects and therefore its use in women of reproductive age should be carefully considered and undertaken only with “double” contraceptive measures and written informed consent. No single tablet available When used in patients with integrase resistance or combined with certain other medications, requires twice-a-day dosing
Dolutegravir + lamivudine (Dovato)	Only recommended initial two-drug regimen Single pill once-a-day regimen	Not for use in patients with HIV RNA > 500,000 copies/mL, or patients initiating therapy during an opportunistic infection, or patients with hepatitis B coinfection, or patients in whom ART is being started prior to results of HIV genotypic resistance testing or hepatitis B testing. Dolutegravir has an increased risk of infant neural tube defects, and therefore, its use in women of reproductive age should be carefully considered and undertaken only with “double” contraceptive measures and written informed consent.
Other Integrase Inhibitor Regimens		
Dolutegravir + abacavir + lamivudine (Triumeq)	Single pill once-a-day regimen Low risk of resistance Superior to Atripla Dolutegravir plus either abacavir/lamivudine or emtricitabine/TDF is superior to darunavir/ritonavir plus either of the NRTI backbones	Dolutegravir has an increased risk of infant neural tube defects, and therefore, its use in premenopausal women should be carefully considered and undertaken only with “double” contraceptive measures and written informed consent. Abacavir should be used only in HLA-B*5701-negative persons Should not be used in patients with hepatitis B coinfection When used in patients with integrase resistance or combined with certain other medications, requires twice-a-day dosing Fixed-dose combination should not be used in patients with creatinine clearance < 50 mL/min
Raltegravir (400 mg twice daily) + Either: emtricitabine/TDF or emtricitabine/TAF or lamivudine/TDF or lamivudine/TAF	Preferred integrase inhibitor for women who want to become pregnant Fewest drug interactions of integrase inhibitors	Lower barrier to resistance than bictegravir and dolutegravir Requires twice-a-day dosing No single tablet available
Alternative Initial Regimens for Patients Who Cannot Take an Integrase Inhibitor		
Darunavir (800 mg daily) with cobicistat + Either: emtricitabine/TDF or emtricitabine/TAF or lamivudine/TDF or lamivudine/TAF (boosted protease inhibitor regimen)	Single tablet once-a-day regimen (with emtricitabine and TAF, Symtuza)	Cobicistat boosting causes similar drug-drug interactions as ritonavir; increases in serum creatinine (nonpathologic)

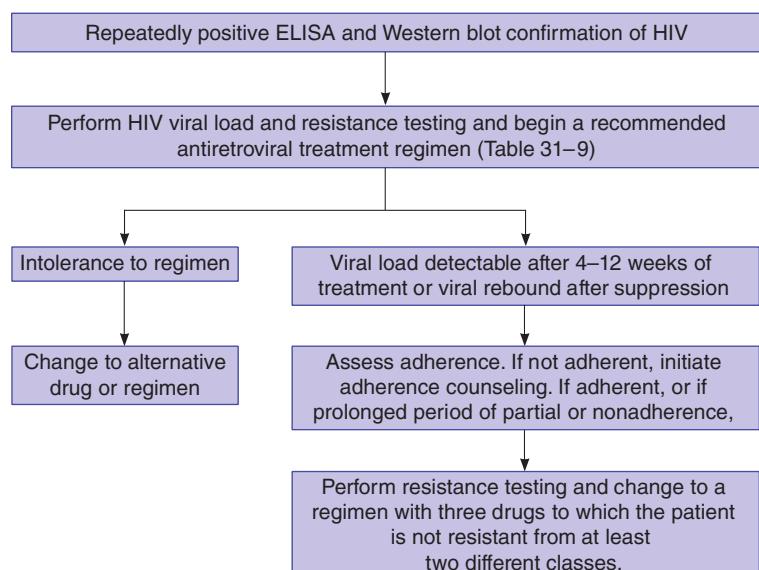
(continued)

Table 31–9. Recommended and alternative initial antiretroviral therapy (ART) regimens (alphabetical order). (continued)

Regimen	Advantages	Disadvantages
Alternative Initial Regimens for Patients Who Cannot Take an Integrase Inhibitor (cont.)		
Darunavir (800 mg daily) with ritonavir (100 mg daily) boosting + Either: emtricitabine/TDF or emtricitabine/TAF or lamivudine/TDF or lamivudine/TAF (boosted protease inhibitor regimen)	Potent boosted PI Can be given once daily Limited risk of resistance with poor adherence	Not available as a single tablet May cause rash in patients with sulfa allergy Ritonavir boosting required Has metabolic side effects
Doravirine with Either: emtricitabine/TDF or emtricitabine/TAF or lamivudine/TDF or lamivudine/TAF	Avoids the use of both integrase inhibitors and protease inhibitors Available as a single pill with lamivudine and TDF (Delstrigo) Does inhibit or induce the cytochrome P450 3A4 enzyme	In cases of viral virologic failure, NNRTI cross-resistance may develop.
Efavirenz/emtricitabine/TDF (Atripla) Efavirenz/lamivudine/TDF Non-integrase, non-protease inhibitor regimens	Single tablet once-a-day regimen with emtricitabine Longest-term clinical experience Highly effective across broad range of initial CD4 counts and viral loads	Avoid in patients with transmitted <i>K103N</i> resistance Neuropsychiatric symptoms common and can be persistent
Rilpivirine/emtricitabine/TDF (Complera) or with emtricitabine/TAF (Odefsey) Non-integrase, non-protease inhibitor regimens	Single tablet once-a-day regimens Noninferior to Atripla in patients with baseline viral load < 100,000/mcL Limited metabolic side effects	Requires taking with a meal Cannot be used with proton pump inhibitors Use only in patients with viral loads < 100,000 copies/mL and CD4 counts > 200 cells/mcL Do not use in patients with viral loads > 100,000 copies/mL or CD4 counts < 200 cells/mcL

¹Usual medication doses are supplied when not part of a fixed-dose preparation.

TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

**Figure 31–7.** Approach to monitoring initial and subsequent antiretroviral therapy.

resistance testing, and assessment of the patient's ability to comply with complicated regimens or to tolerate predictable side effects, the clinician should prescribe a combination of three medications to which there is no or only minimal resistance.

Once antiretroviral treatment has been initiated, it is not advisable to stop the therapy unless there is a compelling reason (eg, toxicity, poor adherence, etc). So-called drug holidays or structured treatment interruptions are not recommended because they have been shown to increase risk of AIDS-related complications, increase CD4 declines, and increase morbidity from non-AIDS-related complications (eg, myocardial infarctions and liver failure).

3. The challenge of medication resistance—Resistance to HIV-1 medication has been documented for all currently available antiretrovirals including the newer classes of fusion inhibitor, CCR5 inhibitors, and integrase inhibitors. Although HIV medication resistance was common in the past, high-level resistance has been declining in the past few years, likely related to better tolerated, easier to use, and more efficacious antiretroviral agents. Resistance also occurs in patients who are antiretroviral treatment-naïve but who are infected with a medication-resistant strain—called “primary” or “transmitted” medication resistance. Cohort studies of antiretroviral treatment-naïve patients entering care in North America and Western Europe show that roughly 10–12% (and sometimes as high as 25%) of recently infected individuals have been infected with a medication-resistant strain of HIV-1.

In addition to being part of a standard baseline evaluation, resistance testing is recommended for patients who are receiving antiretroviral treatment and have suboptimal viral suppression (ie, viral loads greater than 200 copies/mL). Both genotypic and phenotypic resistance tests are commercially available and in randomized controlled studies their use has been shown to result in improved short-term virologic outcomes compared to making treatment choices without resistance testing. Furthermore, multiple retrospective studies have conclusively demonstrated that resistance tests provide prognostic information about virologic response to newly initiated therapy that cannot be gleaned from standard clinical information (ie, treatment history, examination, CD4 count, and viral load tests).

Because of the complexity of resistance tests, many clinicians require expert interpretation of results. In the case of genotypic assays, results may show that the mutations that are selected for during antiretroviral treatment are medication-specific or contribute to broad cross-resistance to multiple medications within a therapeutic class. An example of a medication-specific mutation for the reverse transcriptase inhibitors would be the *M184V* mutation that is selected for by lamivudine or emtricitabine therapy—this mutation causes resistance only to those two medications. Conversely, the thymidine analog mutations (“TAMs”) of *M41L*, *D67N*, *K70R*, *L210W*, *T215Y/F*, and *T219Q/K/E* are selected for by either zidovudine or stavudine therapy, but cause resistance to all the medications in the class and often extend to the nucleotide inhibitor tenofovir when three or more of these TAMs are present. Further complicating the

interpretation of genotypic tests is the fact that some mutations that cause resistance to one medication can actually make the virus that contains this mutation more sensitive to another medication. The *M184V* mutation, for example, is associated with increased sensitivity to zidovudine, stavudine, and tenofovir. The most common mutations associated with medication resistance and cross-resistance patterns for NRTIs, NNRTIs, PIs, and integrase inhibitors can be found at <https://hivdb.stanford.edu> (see specific references below). Phenotypic tests also require expert interpretation in that the distinction between a resistant virus and sensitive one is not fully defined for all available medications.

Furthermore, both methods of resistance testing are limited by the fact that they may measure resistance in only some of the viral strains present in an individual. Resistance results may also be misleading if a patient is not taking antiretroviral medications at the time of testing because the dominant virus is likely the wild-type, even if there are resistant viruses in the body that can become dominant with the selective pressure of antivirals. Thus, resistance results do not replace a careful history of what medications a patient has taken in the past and for how long. Also, the results of resistance testing should be viewed cumulatively—ie, if resistance is reported to an agent on one test, it should be presumed to be present thereafter even if subsequent tests do not give the same result.

Stanford University HIV Drug Resistance Database Home Page (<https://hivdb.stanford.edu/>) provides Genotypic Resistance Interpretation Algorithm, HIVdb Program, version 9.0, February 22, 2021 (<https://hivdb.stanford.edu/hivdb/by-mutations/>); Genotype-Phenotype Correlations (<https://hivdb.stanford.edu/pages/genotype-phenotype.html>); Genotype-Treatment Correlations (<https://hivdb.stanford.edu/pages/genotype-rx.html>); Genotype-Clinical Outcome Correlations (<https://hivdb.stanford.edu/pages/genotype-clinical.html>)

F. Constructing Antiretroviral Treatment Regimens for Patients with Resistance

In designing second-line regimens for patients with resistance to initial therapy, the goal is to identify three medications from at least two different classes to which the virus is not resistant. Even without resistance testing, certain forms of cross-resistance between medications within a class can be assumed. For example, the resistance patterns of lopinavir/ritonavir and indinavir are overlapping, and patients with virus resistant to these agents are unlikely to respond to nelfinavir or saquinavir even though they have never received treatment with these agents. Similarly, the resistance patterns of nevirapine and efavirenz are overlapping—as are the resistance patterns between raltegravir and elvitegravir. Fostemsavir, an attachment inhibitor, and ibalizumab, a monoclonal antibody, are specifically FDA approved for heavily treated adults with multidrug-resistant HIV who are not responding to their existing regimen. They are used in combination with other antiretroviral drugs.

In constructing regimens, toxicities should be nonoverlapping and agents that are either virologically antagonistic

or incompatible in terms of drug-drug interactions should be avoided. For example, the combination of stavudine plus didanosine should be avoided, since there is increased risk of toxicities, in particular in pregnant women because of the increased risk of lactic acidosis, which can be fatal. Moreover, the nucleoside pair of zidovudine and stavudine should be avoided because of increased toxicity and the potential for antagonism that results from intracellular competition for phosphorylation. The combination of didanosine with tenofovir should be avoided because of observed declines in CD4 counts. Etravirine should not be used with boosted tipranavir because of drug-drug interactions. Lamivudine and emtricitabine are essentially the same medication and so are not used together.

Given the availability of new class medications and new generation medications, a combination of antiretroviral treatment can successfully treat virtually all patients—no matter how much resistance is present.

► Course & Prognosis

With improvements in therapy, patients who are compliant with treatment should have near normal life spans. A population-based study conducted in Denmark found that HIV-infected persons at age 25 years without hepatitis C had a life expectancy similar to that of an uninfected 25-year-old. Unfortunately, not all HIV-infected persons have access to treatment. Studies consistently show less access to treatment for Blacks, the homeless, and injection drug users. For patients whose disease progresses even though they are receiving appropriate treatment, palliative care must be provided (see Chapter 5), with attention to pain control, spiritual needs, and family (biologic and chosen) dynamics.

► When to Refer

- HIV-infected patients in whom viral loads cannot be fully suppressed on one of the initial recommended regimens should be referred to specialists.
- Specialty consultation is particularly important for those patients with detectable viral loads on antiretroviral treatment; those intolerant of standard medications; those in

need of systemic chemotherapy; and those with complicated opportunistic infections, particularly when invasive procedures or experimental therapies are needed.

► When to Admit

Admit patients with opportunistic infections who are acutely ill (eg, who are febrile, who have had rapid change of mental status, or who are in respiratory distress) or who require intravenous medications.

Cahn P et al; GEMINI Study Team. Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naïve adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. *Lancet*. 2019;393:143. [PMID: 30420123]

Emu B et al. Phase 3 study of ibalizumab for multidrug-resistant HIV-1. *N Engl J Med*. 2018;379:645. [PMID: 30110589]

Gallant J et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicenter, phase 3 randomised controlled non-inferiority trial. *Lancet*. 2017;390:2063. [PMID: 28867497]

Kozal M et al. Fostemsavir in adults with multidrug-resistant HIV-1 infection. *N Engl J Med*. 2020;382:1232. [PMID: 32212519]

Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/Adult_OI.pdf. Updated 2020 May 26.

Saag MS et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2020 recommendations of the International Antiviral Society-USA Panel. *JAMA*. 2020;324:1651. [PMID: 33052386]

Swindells S et al. Long-acting cabotegravir and rilpivirine for maintenance of HIV-1 suppression. *N Engl J Med*. 2020;382:1112. [PMID: 32130809]

Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/Adult_OI.pdf. Updated 2020 May 26.

32

Viral & Rickettsial Infections

Eva Clark, MD, PhD

Christine Akamine, MD

Wayne X. Shandera, MD

VIRAL DISEASES

HUMAN HERPESVIRUSES

1. Herpesviruses 1 & 2



ESSENTIALS OF DIAGNOSIS

- ▶ Spectrum of illness: stomatitis, urogenital lesions, Bell palsy, encephalitis.
- ▶ Variable intervals between exposure and clinical disease since herpes simplex virus (HSV) causes both primary (often subclinical) and reactivation disease.

► General Considerations

HSV-1 and HSV-2 affect primarily the oral and genital areas, respectively. Asymptomatic shedding of either virus is common, but it is more common with HSV-2 and from genital areas, with most infected individuals shedding virus at least once a month, which may be responsible for transmission. Asymptomatic HSV-2-infected individuals shed the virus less often than those with symptomatic infection. Clinical disease typically indicates reactivation. Total and subclinical shedding of HSV-2 virus decrease after the first year of initial infection, although viral shedding continues for years thereafter.

Although HSV-2 is the most common cause of genital ulcers in the developed world, epidemiologic studies show that HSV-1 is a more common cause of both genital and oral lesions than HSV-2 in young women in the United States. Most HSV-2-infected persons in the United States are unaware that they are infected.

HSV-2 seropositivity is associated with higher risk of HIV acquisition (it is threefold higher among persons who are HSV-2 seropositive than among those who are HSV-2 seronegative), and HSV-2 reactivates more often in advanced HIV infection. HIV replication is increased by interaction with HSV proteins. Suppression of HSV-2

decreases HIV plasma levels and genital tract shedding of HIV, which can contribute to a reduction in the sexual transmission of HIV.

► Clinical Findings

A. Symptoms and Signs

1. Mucocutaneous disease—See Chapter 6 for HSV-1 mucocutaneous disease (“herpes labialis” or “gingivostomatitis”). Digital lesions (whitlows) (Figure 32-1) are an occupational hazard in medicine and dentistry. Contact sports (eg, wrestling) are associated with outbreaks of skin infections (“herpes gladiatorium”).

Vesicles form moist, painful ulcers after several days and epithelialize over 1–2 weeks if untreated. Primary infection is usually more severe than recurrences but may be asymptomatic. Recurrences often involve fewer lesions, tend to be labial, heal faster, and are triggered by stress, fever, infection, sunlight, chemotherapy (eg, fludarabine, azathioprine), among other undetermined factors.

HSV-2 lesions largely involve the genital tract. The virus typically remains latent in the presacral ganglia and shedding of HSV-2 can occur for years after acquisition (see Chapter 6). Occasionally, lesions arise in the perianal region or on the buttocks and upper thighs. Dysuria, cervicitis, and urinary retention may occur in women. Urethritis may occur in men. Proctitis and extensive, ulcerating, weeping sacral lesions may be presenting symptoms in people living with HIV infection with low CD4 counts. Large ulcerations and atypical lesions suggest drug-resistant isolates.

2. Ocular disease—HSV can cause uveitis, keratitis, blepharitis, and keratoconjunctivitis (see Chapter 7). Lesions limited to the epithelium usually heal without affecting vision, whereas stromal involvement can cause uveitis, scarring, and eventually blindness. HSV is the second most common infectious cause of acute retinal necrosis, after varicella-zoster virus (VZV).

3. Neonatal and congenital infection—Rarely, either HSV-1 or HSV-2 can infect the fetus and induce congenital malformations (organomegaly, bleeding, and central nervous system [CNS] abnormalities). Neonatal transmission during delivery, however, is more common than



▲ Figure 32–1. Herpetic whitlow. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)

intrauterine infection. The global rate of neonatal herpes is estimated to be about 10 cases per 100,000 live births. Maternal infection during the third trimester is associated with the highest risk of neonatal transmission, but about 70% of these infections are asymptomatic or unrecognized. Invasive fetal monitoring and vacuum or forceps delivery increase the risk of herpesvirus transmission.

4. CNS disease—Traditionally, herpes simplex encephalitis is associated with HSV-1 infection and aseptic meningitis with HSV-2 infection. Both viruses, however, can cause encephalitis. Encephalitis presents with nonspecific symptoms: a flu-like prodrome, followed by headache, fever, behavioral and speech disturbances, and focal or generalized seizures. The temporal lobe is often involved. Untreated disease and presentation with coma carry a high mortality. Ischemic stroke, although infrequent, can complicate the course of HSV meningitis or encephalitis, or can happen in isolation due to HSV-induced cerebral vasculitis. Many survivors suffer neurologic sequelae, which are observed more frequently among patients with HSV-1 infection. Both HSV-1 and HSV-2 can cause mild, nonspecific neurologic symptoms and are also associated with benign recurrent lymphocytic (Mollaret) meningitis. Hyponatremia is a predictive marker for encephalitis before lumbar puncture data are available.

5. Disseminated infection—Disseminated HSV infection occurs in the setting of immunosuppression, either primary or iatrogenic, or rarely with pregnancy. In disseminated disease, skin lesions are not always present. Disseminated skin lesions are a particular complication in patients with atopic eczema (*eczema herpeticum*) and burns. Pneumonia can occur regardless of immune status.

6. Bell palsy—HSV-1 is a cause of Bell palsy (facial nerve paralysis) (see also Chapter 24).

7. Esophagitis and proctitis—HSV-1 can cause esophagitis in immunocompromised patients, particularly those with AIDS. The lesions are smaller and deeper than those

observed in patients with cytomegalovirus (CMV) esophagitis or with other herpesviruses known to cause esophagitis in immunocompromised persons. Rarely HSV esophagitis is accompanied by significant upper gastrointestinal hemorrhage. Proctitis occurs mainly in men who have sex with men.

8. Erythema multiforme—Herpes simplex viruses are a leading cause of erythema multiforme minor (“herpes-associated erythema multiforme”) and of the more severe condition Stevens-Johnson syndrome/toxic epidermal necrolysis (see also Chapter 6).

9. Other—HSV infection causes approximately 1% of cases of acute liver failure, particularly in pregnant women and immunosuppressed patients. The mortality of such rare fulminant hepatitis is nearly 75%. An HSV lower respiratory tract infection of unknown clinical significance is common in mechanically ventilated patients. Evidence suggests that this finding is usually an indicator rather than the cause of a poor clinical condition. HSV-1 pneumonia is associated with high morbidity in patients with solid tumors. HSV-1 is reported to be a cause of perinephric abscess, febrile neutropenia, chronic urticaria, and esophagitis and enteritis in systemic lupus erythematosus. HSV is also associated with *Helicobacter pylori*-negative upper gastrointestinal tract ulcers.

B. Laboratory Findings

1. Mucocutaneous disease—See Chapter 6.

2. Ocular disease—Herpes keratitis is diagnosed by branching (dendritic) ulcers that stain with fluorescein. The extent of epithelial injury in herpes keratitis correlates well with polymerase chain reaction (PCR) positivity. Uveitis from HSV is often diagnosed clinically, although PCR assays (including a new multiplex assay that includes VZV) on anterior chamber aspirated material may assist in making the diagnosis.

3. Encephalitis and recurrent meningitis—Cerebrospinal fluid (CSF) pleocytosis is common, with a similar increase in the number of red cells although CSF findings may be atypical in immunosuppressed patients. HSV real-time PCR of the CSF is a rapid, sensitive, and specific tool for early diagnosis and can be included in a multiple rapid array panel. Viral detection by this method can be used if the clinical picture is consistent, especially if initial studies are negative. Antibodies to HSV in CSF can confirm the diagnosis but appear late in disease. Viral culture shows a sensitivity of only 10%. MRI scanning is often a useful adjunct showing increased signal in the temporal and frontal lobes. Temporal lobe seizure foci may be shown on electroencephalograms (EEGs). Atypical presentations for HSV encephalitis are reported from Germany including the absence of pleocytosis, unremarkable early CT presentations, and unusual MRI findings (global edema).

4. Esophagitis, proctitis, and other gastrointestinal disease—Esophagitis is diagnosed by endoscopic biopsy with real-time PCR and cultures. Proctitis may be diagnosed by rectal swab for PCR, culture, or both. Complicated cases may require biopsy. Concomitant hepatitis and colitis have

been reported with herpes simplex. In pregnancy, HSV hepatitis is infrequently (18% in one series) associated with a rash and carries a mortality up to 39%.

5. Pneumonia—Pneumonia is diagnosed by clinical, pathologic, and radiographic findings. The CT findings include diffuse or multifocal areas of ground-glass attenuation or consolidative changes or both and are best confirmed by using high-resolution CT techniques.

► Treatment & Prophylaxis

Medications that inhibit replication of HSV-1 and HSV-2 include acyclovir and related compounds, foscarnet, cidofovir, and trifluridine and vidarabine (both for keratitis) (Table 32–1). Agents under study include helicase-primease inhibitors (pritelivir) with promising preliminary data. Brincidofovir, a lipid conjugate of cidofovir, shows in vitro activity against HSV/VZV and is effective in preliminary studies in hematopoietic cell transplant recipients as HSV/VZV prophylaxis.

A. Mucocutaneous Disease

See Chapter 6.

B. Keratitis and Uveitis

For the treatment of acute epithelial keratitis, oral antiviral agents such as valacyclovir or famciclovir are first-line therapies (see Chapter 7). The usage of topical corticosteroids may exacerbate the infection, although systemic corticosteroids may help with selected cases of stromal infection. Long-term treatment (more than 1 year) with acyclovir at a dosage of 800 mg/day orally decreases recurrence rates of keratitis, conjunctivitis, or blepharitis due to HSV.

Uveitis is best managed with oral systemic (not topical) acyclovir, although HSV resistance among people living with HIV infection is reported because of the diversity of the HSV species often present.

C. Neonatal Disease

Counseling (but not serologic screening) should be offered to pregnant mothers. The use of maternal antenatal suppressive therapy with acyclovir (typically, 400 mg orally three times daily) beginning at 36 weeks' gestation decreases the presence of detectable HSV, the rates of recurrence at delivery, and the need for cesarean delivery. Cesarean delivery is recommended for pregnant women with active genital lesions or typical prodromal symptoms.

D. Encephalitis and Meningitis

Because of the need for rapid treatment to decrease mortality and neurologic sequelae, intravenous acyclovir (10 mg/kg every 8 hours for 10 days or more, adjusting for kidney disease) should be started in those patients with suspected HSV encephalitis, stopping only if another diagnosis is established. If the PCR of CSF is negative but clinical suspicion remains high, treatment should be continued for 10 days because the false-negative rate for PCR can be as high as 25% (especially in children) and acyclovir is

relatively nontoxic. Acyclovir resistance in a case of herpes simplex encephalitis is reported. Herpes simplex viral load does not appear to correlate with outcome of meningitis, and it is not recommended to follow viral load over time.

Long-term neurologic sequelae of HSV encephalitis are common, and late pediatric relapse is recognized. Aseptic meningitis may also require a course of intravenous acyclovir or valacyclovir. Long-term oral prophylaxis with valacyclovir, however, does not appear to prevent recurrences of aseptic meningitis with HSV-2.

E. Disseminated Disease

Disseminated disease responds best to parenteral acyclovir when treatment is initiated early.

F. Bell Palsy

Prednisolone, 25 mg orally twice daily for 10 days started within 72 hours of onset, significantly increases the rate of recovery. Data on antiherpes agents are equivocal, and therefore, HSV assays are not routinely recommended; according to one study, valacyclovir (but not acyclovir), 1 g orally daily for 5 days, plus corticosteroid therapy may be beneficial if started within 7 days of symptom onset. In patients with severe or complete facial paralysis, such antiviral therapy is often administered but without proof of efficacy.

G. Esophagitis and Proctitis

Patients with esophagitis should receive either intravenous acyclovir (5–10 mg/kg every 8 hours) or oral acyclovir (400 mg five times daily) through resolution of symptoms, typically 3–5 days; however, longer treatment may be necessary for immunosuppressed patients. Maintenance therapy for AIDS patients is also with acyclovir (400 mg orally three to five times daily). Proctitis is treated with similar dosages and usually responds within 5 days, although in HIV-infected patients, higher doses (up to 5 g/day) intravenously in five or six divided doses may be needed for severe lesions.

H. Erythema Multiforme

Suppressive therapy with oral acyclovir (400 mg twice a day for 6 months) decreases the recurrence rate of HSV-associated erythema multiforme. Valacyclovir (500 mg orally twice a day) may be effective in cases unresponsive to acyclovir.

► Prevention

Besides antiviral suppressive therapy (see Erythema multiforme, above and in Chapter 6), prevention also requires counseling and the use of condom barrier precautions during sexual activity. Disclosure to sexual partners of HSV-seropositive status is associated with about a 50% reduction in HSV-2 acquisition. Male circumcision is associated with a lower incidence of acquiring HSV-2 infection.

Preventing spread to hospital staff and other patients from cases with mucocutaneous, disseminated, or genital disease requires isolation and usage of hand washing and gloving-gowning precautions. Staff with active lesions (eg, whitlows) should not have contact with patients. There is no approved herpes vaccine. Other vaccine candidates are

Table 32–1. Agents for viral infections (listed in alphabetical order).¹

Drug	Dosing ²	Spectrum	Toxicities
Acyclovir	HSV and VZV infections: 400 mg orally three times daily or 200 mg orally five times daily; 30 mg/kg/day or 10 mg/kg every 8 hours intravenously for 7 days Acute herpes encephalitis: 10 mg/kg intravenously every 8 hours for 14–21 days	HSV, VZV	Neurotoxic reactions, reversible kidney dysfunction, local reactions
Baloxavir	40 mg dose if patient is 40 to < 80 kg 80 mg if patient is ≥ 80 kg Only use for patients 12 years and older	Influenza A and B strains	Diarrhea and bronchitis
Cidofovir	5 mg/kg intravenously weekly for 2 weeks, then every other week	CMV	Neutropenia, kidney disease, ocular hypotonia
Famciclovir	Acute VZV: 500 mg orally three times daily for 7 days Genital or cutaneous HSV-1/HSV-2: 250 mg three times daily for 7–10 days; 125 mg twice daily for 5 days for recurrences (500 mg twice daily for 7 days if HIV-positive)	HSV, VZV	Early angioedema; later rarely, gastrointestinal symptoms, headaches, rashes
Foscarnet	Induction: 90 mg/kg intravenously (90- to 120-minute infusion) every 12 hours or 60 mg/kg intravenously (minimum 1-hour infusion) every 8 hours over 2–3 weeks depending on clinical response Maintenance: 90–120 mg/kg intravenously (2-hour infusion) once daily	HSV resistant to acyclovir, CMV, VZV, HIV-1	Nephrotoxicity, genital ulcerations, calcium disturbances
Ganciclovir	Induction: 5 mg/kg intravenously every 12 hours for 14–21 days Maintenance: 6 mg/kg/day intravenously for 5 days each week	CMV	Neutropenia, thrombocytopenia, CNS side effects
Iodoxuridine	Topical, 0.1% every 1–2 hours for 3–5 days (not available in the United States)	HSV keratitis	Local reactions
Interferon alfa-2b	HBV infection: 10 million international units subcutaneously three times weekly or 5 million units daily ¹ Condylomata: 1 million international units intralesionally in up to five warts three times weekly for 3 weeks	HBV, HCV, HPV	Influenza-like syndrome, myelosuppression, neurotoxicity
Interferon alfa-n3	Refractory or recurring external condylomata acuminata: 0.05 mL (250,000 international units) per wart intralesionally twice weekly for up to 8 weeks; 0.5 mL (2.5 million international units) is the maximum dose per treatment session	HPV, HCV	Local reactions Influenza-like syndrome, myelosuppression, neurotoxicity
Oseltamivir	75 mg orally twice daily for 5 days	Influenza A and B	Dose needs to be adjusted for kidney dysfunction
Palivizumab	15 mg/kg intramuscularly every month in RSV season	RSV	Upper respiratory infection symptoms
Penciclovir	Topical 1% cream every 2 hours for 4 days	HSV	Local reactions
Peramivir	Intravenous, 600-mg single dose	Uncomplicated influenza A	Nausea, vomiting, diarrhea, neutropenia
Remdesivir	Intravenous, 200 mg first day followed by 100 mg/day for 4 days for non-ICU patients, 9 more days for ICU patients	Coronavirus-19 (COVID-19)	Transaminitis, fatigue, headaches, nausea
Ribavirin	RSV infection: one vial (6 g) dissolved and delivered through a Small Particle Aerosol Generator (SPAG-2) over a continuous 12- to 18-hour period daily for 5 consecutive days	RSV, severe influenza A or B, Lassa fever	Wheezing, hemolytic anemia
Trifluridine	Topical, 1% drops every 2 hours to 9 drops/day	HSV keratitis	Local reactions
Valacyclovir	Acute VZV: 1 g orally three times daily for 7 days Primary genital HSV-1/HSV-2: 1 g twice daily for 10 days Recurrent genital HSV-1/HSV-2: 500 mg twice daily for 3 days Suppressive therapy: 1 g daily; 500 mg if fewer than 9 recurrences/year (Dose depends on immune status and number of recurrences.)	VZV, HSV	Thrombotic thrombocytopenic purpura or hemolytic-uremic syndrome in AIDS
Valganciclovir	900 mg orally twice daily for 3 weeks; 900 mg daily as maintenance	CMV	See ganciclovir
Zanamivir	5 mg inhalations twice daily for 5 days	Uncomplicated influenza A and B	Bronchospasm in patients with asthma

Sources: Data from Drugs.com and Lexicomp Online.

¹Agents used exclusively in the management of HIV infection and AIDS are found in Chapter 31. Agents used in the management of HBV and HCV infections are found in Chapter 16.

²Dosing varies considerably by indication and may require adjustment based on patient's clinical state and type of viral infection. Consultation with a pharmacist is recommended.

CMV, cytomegalovirus; CNS, central nervous system; CSF, cerebrospinal fluid; HBV, hepatitis B virus; HCV, hepatitis C virus; HPV, human papillomavirus; HSV, herpes simplex virus; RSV, respiratory syncytial virus; VZV, varicella-zoster virus.

in preclinical studies, including a mRNA vaccine against HSV-2 (specifically, this vaccine expresses HSV-2 glycoproteins C, D, and E in lipid nanoparticles) that is targeted toward pregnant women to prevent neonatal herpes.

Dropulic LK et al. A randomized, double-blinded, placebo-controlled, phase 1 study of a replication-defective herpes simplex virus (HSV) type 2 vaccine, HSV529, in adults with or without HSV infection. *J Infect Dis.* 2019;220:990. [PMID: 31058977]

McCormack AL et al. HSV hepatitis in pregnancy: a review of the literature. *Obstet Gynecol Surv.* 2019;74:93. [PMID: 30756123] Pittet LF et al. Postnatal exposure to herpes simplex virus: to treat or not to treat? *Pediatr Infect Dis J.* 2020. [Epub ahead of print] [PMID: 32773663]

Whitley R et al. Clinical management of herpes simplex virus infections: past, present, and future. *F1000Res.* 2018;7:1726. [PMID: 30443341]

Workowski KA et al; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep.* 2015;64:1. [PMID: 26042815]

2. Varicella (Chickenpox) & Herpes Zoster (Shingles)



ESSENTIALS OF DIAGNOSIS

- ▶ **Varicella rash:** pruritic, centrifugal, papular changing to vesicular ("dew drops on a rose petal"), pustular, and finally crusting.
- ▶ **Zoster rash:** tingling, pain, eruption of vesicles in a dermatomal distribution, evolving to pustules and then crusting.

► General Considerations

Disease manifestations of VZV, or human herpesvirus (HHV)-3, include chickenpox (varicella) and shingles (herpes zoster). Chickenpox generally presents during childhood; has an incubation period of 10–20 days (average 2 weeks); and is highly contagious, spreading by inhalation of infective droplets or contact with lesions.

The incidence and severity of herpes zoster ("shingles"), which affects up to 25% of persons during their lifetime, increases with age due to an age-related decline in immunity against VZV. More than half of all patients in whom herpes zoster develops are older than 60 years, and the incidence of herpes zoster reaches 10 cases per 1000 patient-years by age 80 (by which time 50% are infected with VZV). The annual incidence in the United States of 1 million cases is increasing as the population ages. Populations at increased risk for varicella-zoster-related diseases include immunosuppressed persons and persons receiving biologic agents.

► Clinical Findings

A. Varicella

1. Symptoms and signs—Fever and malaise are mild in children and more marked in adults. The pruritic rash begins prominently on the face, scalp, and trunk, and later involves the extremities (Table 32–2). Maculopapules change within a few hours to vesicles that become pustular and eventually form crusts (Figures 32–2 and 32–3). New lesions may erupt for 1–5 days, so that different stages of the eruption are usually present simultaneously. The crusts slough in 7–14 days. The vesicles and pustules are superficial and elliptical, with slightly serrated borders. Pitted

Table 32–2. Diagnostic features of some acute exanthems (listed in alphabetical order).

Disease	Prodromal Signs and Symptoms	Nature of Eruption	Other Diagnostic Features	Laboratory Tests
Atypical measles	Same as measles.	Maculopapular centripetal rash, becoming confluent.	History of measles vaccination.	Measles antibody present in past, with titer rise during illness.
Chikungunya fever	2–4 (sometimes 1–12) days, fever, headaches, abdominal complaints, myalgias, arthralgias.	Maculopapular, centrally distributed, pruritus, can be bullous with sloughing in children, occasional facial edema and petechiae.	History of mosquito bites, epidemiologic factors.	ELISA-based IgM or IgG (fourfold increase in titers); PCR and cultures are infrequently available.
Eczema herpeticum	None.	Vesiculopustular lesions in area of eczema.		HSV isolated in cell culture. Multinucleated giant cells in smear of lesion.
Ehrlichiosis	Headache, malaise.	Rash in one-third, similar to Rocky Mountain spotted fever.	Pancytopenia, elevated liver biochemical tests.	PCR, immunofluorescent antibody.
Enterovirus infections	1–2 days of fever, malaise.	Maculopapular rash resembling rubella, rarely papulovesicular or petechial.	Aseptic meningitis.	Virus isolation from stool or CSF; complement fixation titer rise.

(continued)

Table 32–2. Diagnostic features of some acute exanthems (listed in alphabetical order). (continued)

Disease	Prodromal Signs and Symptoms	Nature of Eruption	Other Diagnostic Features	Laboratory Tests
Erythema infectiosum (erythrovirus)	None. Usually in epidemics.	Red, flushed cheeks; circumoral pallor; maculopapules on extremities.	"Slapped face" appearance.	White blood cell count normal.
Exanthema subitum (HHV-6, 7; roseola)	3–4 days of high fever.	As fever falls, pink maculopapules appear on chest and trunk; fade in 1–3 days.		White blood cell count low.
Infectious mononucleosis (EBV)	Fever, adenopathy, sore throat.	Maculopapular rash resembling rubella, rarely papulovesicular.	Splenomegaly, tonsillar exudate.	Atypical lymphocytes in blood smears; heterophile agglutination (Monospot test).
Kawasaki disease	Fever, adenopathy, conjunctivitis.	Cracked lips, strawberry tongue, maculopapular polymorphous rash, peeling skin on fingers and toes.	Edema of extremities. Angitis of coronary arteries.	Thrombocytosis, electrocardiographic changes.
Measles (rubeola)	3–4 days of fever, coryza, conjunctivitis, and cough.	Maculopapular, brick red; begins on head and neck; spreads downward and outward, in 5–7 days rash brownish, desquamating. See Atypical measles, above.	Koplik spots on buccal mucosa.	White blood cell count low. Virus isolation in cell culture. Antibody tests by hemagglutination inhibition or neutralization.
Meningococcemia	Hours of fever, vomiting.	Maculopapules, petechiae, purpura.	Meningeal signs, toxicity, shock.	Cultures of blood, CSF. White blood cell count high.
Rocky Mountain spotted fever	3–4 days of fever, vomiting.	Maculopapules, petechiae, initial distribution centripetal (extremities to trunk, including palms).	History of tick bite.	Indirect fluorescent antibody; complement fixation.
Rubella	Little or no prodrome.	Maculopapular, pink; begins on head and neck, spreads downward, fades in 3 days. No desquamation.	Lymphadenopathy, postauricular or occipital.	White blood cell count normal or low. Serologic tests for immunity and definitive diagnosis (hemagglutination inhibition).
Scarlet fever	One-half to 2 days of malaise, sore throat, fever, vomiting.	Generalized, punctate, red; prominent on neck, in axillae, groin, skin folds; circumoral pallor; fine desquamation involves hands and feet.	Strawberry tongue, exudative tonsillitis.	Group A beta-hemolytic streptococci in cultures from throat; antistreptolysin O titer rise.
Smallpox	Fever, malaise, prostration.	Maculopapules to vesicles to pustules to scars (lesions develop at the same pace).	Centrifugal rash; fulminant sepsis in small percentage of patients, gastrointestinal and skin hemorrhages.	Contact CDC ¹ for suspicious rash; EM and gel diffusion assays.
Typhus	3–4 days of fever, chills, severe headaches.	Maculopapules, petechiae, initial distribution centrifugal (trunk to extremities).	Endemic area, lice.	Complement fixation.
Varicella (chickenpox)	0–1 day of fever, anorexia, headache.	Rapid evolution of macules to papules, vesicles, crusts; all stages simultaneously present; lesions superficial, distribution centripetal.	Lesions on scalp and mucous membranes.	Specialized complement fixation and virus neutralization in cell culture. Fluorescent antibody test of smear of lesions.

¹<https://www.cdc.gov/smallpox/index.html>

CDC, Centers for Disease Control and Prevention; CSF, cerebrospinal fluid; EBV, Epstein-Barr virus; ELISA, enzyme-linked immunosorbent assay; EM, electron microscopy; HHV, human herpesvirus; HSV, herpes simplex virus; Ig, immunoglobulin; PCR, polymerase chain reaction.



▲ **Figure 32–2.** Primary varicella (chickenpox) skin lesions. (Public Health Image Library, CDC.)



▲ **Figure 32–3.** Chickenpox (varicella) with classic "dew drop on rose petal" appearance. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)

scars are frequent. Although the disease is often mild, complications (such as secondary bacterial infection, pneumonitis, and encephalitis) occur in about 1% of cases and often lead to hospitalization.

Varicella is more severe in older patients and immunocompromised persons. In the latter, atypical presentations, including widespread dissemination in the absence of skin lesions, are often described. After the primary infection, the virus remains dormant in cranial nerve sensory ganglia and spinal dorsal root ganglia. *Latent VZV will reactivate as herpes zoster in about 10–30% of persons.* There is a small increased risk of Guillain-Barré syndrome for at least 2 months after an acute herpes zoster attack.

2. Laboratory findings—Diagnosis is usually made clinically, with confirmation by direct immunofluorescent antibody staining or PCR of scrapings from lesions, both of which are more sensitive than culture. Multinucleated giant cells are usually apparent on a Tzanck smear of material from the vesicle base. Leukopenia and subclinical transaminase elevation are often present, and thrombocytopenia occasionally occurs. Although elevation of varicella IgM is occasionally used to diagnose a primary VZV infection, the assay has poor performance and is generally not recommended. The exception is that varicella antibody tested in the CSF is useful for identifying CNS involvement if VZV vasculopathy is suspected but CSF VZV DNA PCR is negative. A varicella skin test and interferon-gamma enzyme-linked immunospot (ELISPOT) can screen for VZV susceptibility.

B. Herpes Zoster

Herpes zoster ("shingles") usually occurs among adults, but cases are reported among infants and children. Shingles incidence rises markedly with age because of immunosenescence and loss of specific immunity to VZV, with rates of 8 to 12 per 1000 person-years in individuals older than 80 years. Skin lesions resemble those of chickenpox. Pain is often severe and commonly *precedes* the appearance of rash. Lesions follow a dermatomal distribution, with thoracic and lumbar roots being the most common. In most cases, a single unilateral dermatome is involved, but occasionally, neighboring and distant areas are involved. Lesions on the tip of the nose, inner corner of the eye, and root and side of the nose (**Hutchinson sign**) indicate involvement of the trigeminal nerve (**herpes zoster ophthalmicus**). Facial palsy and lesions of the external ear with or without tympanic membrane involvement, vertigo and tinnitus, or deafness signify geniculate ganglion involvement (**Ramsay Hunt syndrome** or **herpes zoster oticus**). Shingles is a particularly common and serious complication among immunosuppressed patients.

► Complications

A. Varicella

Secondary bacterial skin superinfections, particularly with group A *Streptococcus* and *Staphylococcus aureus*, are the most common complications. Cellulitis, erysipelas, and scarlet fever are described. Bullous impetigo and necrotizing fasciitis are less often seen. Other associations with

varicella include epiglottitis, necrotizing pneumonia, osteomyelitis, septic arthritis, epidural abscess, meningitis, endocarditis, pancreatitis, giant cell arteritis, inflammatory bowel disease, and purpura fulminans. Toxic shock syndrome can also develop.

Interstitial VZV pneumonia is more common in adults (especially cigarette smokers, people living with HIV, and pregnant women) and may result in acute respiratory distress syndrome (ARDS). After healing, numerous densely calcified lesions are seen throughout the lung fields on chest radiographs.

Historically, neurologic complications developed in about 1 in 2000 children. Cerebellar ataxia occurs at a frequency of 1:4000 in the young. A limited course and complete recovery are the rule. Encephalitis is similarly infrequent, occurs mostly in adults, and is characterized by delirium, seizures, and focal neurologic signs. The rates for both mortality and long-term neurologic sequelae are about 10%. Ischemic strokes in the wake of acute VZV infection present at a mean of 4 months after rashes and may be due to an associated vasculitis. Multifocal encephalitis (described without a rash in solid organ transplant recipients), ventriculitis, myeloradiculitis, arterial aneurysm formation, Ramsay Hunt syndrome, an optic neuritis (with zoster ophthalmicus), and arteritis are also described in immunosuppressed individuals, especially those living with HIV. When seizures develop in immunosuppressed patients, especially those taking corticosteroids, disseminated zoster should be considered.

Clinical hepatitis is uncommon and mostly presents in the immunosuppressed patient but can be fulminant and fatal. Reye syndrome (fatty liver with encephalopathy) also complicates varicella (and other viral infections, especially influenza B virus), usually in childhood, and is associated with aspirin therapy (see Influenza, below).

When contracted during the first or second trimesters of pregnancy, varicella carries a minuscule risk of congenital malformations, including cicatricial lesions of an extremity, growth retardation, microphthalmia, cataracts, chorioretinitis, deafness, and cerebrocortical atrophy. If varicella develops around the time of delivery, the newborn is at risk for disseminated disease. VZV is a greater risk to the pregnant mother.

B. Herpes Zoster

Postherpetic neuralgia occurs in 60–70% of patients who have herpes zoster and are older than 60 years. The pain can be prolonged and debilitating. Risk factors for postherpetic neuralgia include advanced age, female sex, the presence of a prodrome, and severity of rash or pain but not family history.

Other complications include the following: (1) bacterial skin superinfections; (2) herpes zoster ophthalmicus, which occurs with involvement of the trigeminal nerve, is a *sight-threatening complication* (especially when it involves the iris), and is a marker for vasculopathic stroke over the ensuing year (Hutchinson sign is a marker of ocular involvement in people living with HIV); (3) rarely, unilateral ophthalmoplegia; (4) keratitis; (5) involvement of the geniculate ganglion of cranial nerve VII as well as cranial

nerves V, VIII, IX, and X; (6) aseptic meningitis; (7) peripheral motor neuropathy; (8) transverse myelitis, which can become chronic; (9) encephalitis; (10) acute cerebellitis; (11) stroke; (12) vasculopathy; (13) acute retinal necrosis; (14) progressive outer retinal necrosis (largely among people living with HIV); (15) temporal arteritis; and (16) sacral meningoRADICULITIS (Elsberg syndrome). Visceral dissemination in immunocompromised patients is rare and fatal over half the time. VZV is a major cause of Bell palsy in patients who are HSV seronegative.

Diagnosis of neurologic complications requires the detection of VZV DNA in CSF or the detection of VZV DNA in tissue. Diagnosis by examination of saliva may be possible. Zoster sine herpete (pain without rash) can also be associated with most of the above complications. A multiplex assay can help distinguish HSV from VZV for patients with keratitis.

Varicella-zoster increases maternal but not fetal morbidity, and pregnant women should be advised to avoid exposure to VZV.

► Treatment

A. General Measures

In general, patients with varicella should be isolated until primary lesions have crusted. The skin is kept clean. Pruritus can be relieved with antihistamines, calamine lotion, and colloidal oatmeal baths. Fever can be treated with acetaminophen (not aspirin). Fingernails can be closely cropped to avoid skin excoriation and infection.

B. Antiviral Therapy

1. Varicella—Uncomplicated disease in otherwise healthy children and adolescents does not require antiviral therapy. Acyclovir, 20 mg/kg (up to 800 mg per dose) orally four times daily for 5–7 days, should be given within the first 24 hours after the onset of varicella rash and should be considered for patients older than 12 years, secondary household contacts (disease tends to be more severe in secondary cases), patients with chronic cutaneous and cardiopulmonary diseases, and children receiving long-term therapy with salicylates (to decrease the risk of Reye syndrome). *Acyclovir hastens defervescence and healing of lesions but does not impact complication rates.* Famciclovir is not approved for anyone under 18 years of age. Valacyclovir can be given between ages 2 and 18 at a dose of 20 mg/kg (max 1 g) three times daily for 5 days. Nonsteroidal anti-inflammatory drug (NSAID) use in varicella-infected children appears to be associated with an increase in bacterial infections.

In immunocompromised patients, in pregnant women during the third trimester, and in patients with extracutaneous disease (encephalitis, pneumonitis), antiviral therapy with high-dose acyclovir (30 mg/kg/day in three divided doses intravenously for at least 7 days, 10 days for encephalitis) should be started once the diagnosis is suspected. The oral alternative is 800 mg four times daily for 5–10 days, based on disease state treated. Corticosteroids may be useful in the presence of pneumonia. Prolonged prophylactic acyclovir is important to prevent VZV

reactivation in profoundly immunosuppressed patients. Adjuvant treatment with VSV-specific immunoglobulins for patients with pneumonia is advocated by some experts.

2. Herpes zoster—For uncomplicated herpes zoster, valacyclovir or famciclovir is preferable to acyclovir due to dosing convenience and higher drug levels in the body (Table 32–1). Therapy should start within the first 72 hours of the onset of the lesions and be continued for 7 days or until the lesions crust over. Amenamevir is an oral helicase-primease inhibitor given as a single dose that is approved to treat shingles in Japan but is not available in the United States. *Antiviral therapy reduces the duration of herpetic lesions and associated episodes of acute pain but does not decrease the risk of postherpetic neuralgia.* Corticosteroids (a tapering course starting at 60 mg/day, for 2–3 weeks) are safe in immunocompetent patients and may be useful in the acute management of disease to hasten the resolution of acute lesions. Corticosteroids do *not* prevent the development of postherpetic neuralgia.

Intravenous acyclovir is used for extradermatomal complications of zoster. Adjunctive therapy may be considered in retinal disease (foscarnet) and acute herpes zoster (sorividine, a topical antiviral). In cases of prolonged or repeated acyclovir use, immunosuppressed patients may require a switch to foscarnet due to the development of acyclovir-resistant VZV infections. VZV associated with the Ramsay Hunt syndrome is more resistant to antiviral therapy.

C. Treatment of Postherpetic Neuralgia

Once established, postherpetic neuralgia is difficult to treat, and less than half of patients achieve adequate pain relief. This condition may respond to neuropathic pain agents such as gabapentin or lidocaine patches. Tricyclic antidepressants and capsaicin cream are also widely used and effective; use of opioids in managing neuropathic pain is controversial and based on limited evidence, and their long-term use should be avoided. The epidural injection of corticosteroids and local anesthetics appears to modestly reduce herpetic pain at 1 month but, as with oral corticosteroids, is not effective for prevention of long-term postherpetic neuralgia. Transcutaneous electrical nerve stimulation or pulsed radiofrequency is reportedly successful. Gabapentin appears to show efficacy as a premedication in reducing the risk of postherpetic neuralgia in diabetic patients with neuropathy.

► Prognosis

The total duration of varicella from onset of symptoms to disappearance of crusts rarely exceeds 2 weeks. Fatalities are rare except in immunosuppressed patients.

Herpes zoster resolves in 2–6 weeks. Antibodies persist longer and at higher levels than with primary varicella. Eye involvement with herpes zoster necessitates periodic future examinations.

► Prevention

Health care workers should be screened for varicella and vaccinated if seronegative. Patients with active varicella or

herpes zoster are promptly separated from seronegative patients. For patients with varicella, airborne and contact isolation is recommended, whereas for those with zoster, contact precautions are sufficient. For immunosuppressed patients with zoster, precautions should be the same as if the patient had varicella. Exposed serosusceptible patients should be placed in isolation and exposed serosusceptible employees should stay away from work for 8–21 days after exposure. Health care workers with zoster should receive antiviral agents during the first 72 hours of disease and withdraw from work until lesions are crusted. The need for postexposure prophylaxis should be assessed.

A. Varicella

1. Vaccination—Universal childhood vaccination against varicella is effective. The varicella vaccine is live and attenuated, safe, and over 98.1% effective when given after 13 months of age. A single antigen live attenuated vaccine (VARIVAX, VARILRIX) or a quadrivalent measles, mumps, rubella, and varicella (MMRV) vaccine (ProQuad) is available (the combination is immunogenic). The first dose of the single antigen vaccine should be administered at 12–18 months of age and the second at 4–6 years. Alternatively, the MMRV vaccine can be given as a first dose at 12–15 months of age and the second dose before elementary school entry. *Aspirin should be avoided for at least 6 weeks after vaccination because of the risk of Reye syndrome.* The single antigen vaccine is safe and well tolerated, but the quadrivalent MMRV vaccine is associated with a small risk of febrile seizures 5–12 days after vaccination among infants aged 12–23 months. Because of this risk, the Centers for Disease Control and Prevention (CDC) recommends using separate varicella and measles, mumps, and rubella (MMR) vaccines for the first dose in children younger than 48 months old. Rashes, when secondary to the varicella vaccine, appear 15–42 days after vaccination. Rare cases of keratitis are associated with zoster and varicella vaccines.

For serosusceptible individuals older than 13 years, two doses of varicella vaccine (single antigen) administered 4–8 weeks apart are recommended. For those who received a single dose in the past, a *catch-up second dose* is advised, especially in the epidemic setting (where it is effective when it can be given during the first 5 days postexposure). Household contacts of immunocompromised patients should adhere to these recommendations. Susceptible pregnant women (who should not be vaccinated with live varicella or zoster vaccines during pregnancy) need to receive the first dose of single antigen vaccine before discharge after delivery and the second dose 4–8 weeks later. The Advisory Committee on Immunization Practices (ACIP) recommends administration of the single agent varicella vaccine as two doses 3 months apart to children living with HIV aged 12 months or older with CD4 cell percentage greater than 15% and adolescents and adults with CD4 cell counts 200 cells/mcL or higher.

The vaccine may also be given to patients with impaired humoral immunity, to patients receiving corticosteroids, to pediatric oncology patients receiving chemotherapy, and to patients with juvenile rheumatoid arthritis who receive

methotrexate. Patients receiving high doses of corticosteroids for over 2 weeks may be vaccinated a month after discontinuation of the therapy. Patients with leukemia, lymphoma, or other malignancies whose disease is in remission and who have not undergone chemotherapy for at least 3 months may be vaccinated. Kidney and liver transplant patients should be vaccinated if they are susceptible to varicella.

The incidence of varicella in the United States is significantly reduced with the varicella vaccine. Although uncommon, the varicella vaccine, like any of the live varicella-zoster vaccines, has the potential to reactivate and cause clinical disease. It is thought that vaccination against varicella provides less protection against future zoster than does natural varicella infection. The incidence of varicella-associated group A streptococcal infection and varicella neurologic complications are both diminished with the advent of varicella vaccination.

The FDA no longer maintains a registry for exposed pregnant women because of the low rate of such incidents and the general safety of varicella vaccines. Incidents can be reported to Merck (877-888-4231) or through the Vaccine Adverse Events Registry System Vaccine (<https://vaers.hhs.gov/index>).

2. Postexposure—Postexposure vaccination is recommended for unvaccinated persons without other evidence of immunity. Varicella-zoster immune globulin available in the United States only as VariZIG should be considered for susceptible exposed patients (for up to 10 days after exposure but as soon as feasible) who cannot receive the vaccine, including immunosuppressed patients, neonates from mothers with varicella around the time of delivery, exposed premature infants born from serosusceptible mothers at greater than 28 weeks of gestation, and neonates born at less than 28 weeks of gestation regardless of maternal serostatus. Varicella and zoster vaccines are not recommended for pregnant women.

No controlled studies have evaluated the use of acyclovir in this setting. VariZIG is given by intramuscular injection in a dosage of 125 international units/10 kg, to a maximum of 625 international units with a weight-based (2-kg cutoff) minimum dose of 62.5 or 125 international units), with a repeat identical dose in 3 weeks if a high-risk patient remains exposed. VariZIG has no place in therapy of established disease; however, it reduces severity of varicella in high-risk children or adults (ie, those with impaired immunity and infants exposed peripartum) if given within 4 days of exposure. Varicella vaccination should be delayed at least 5 months after VariZIG administration. If VariZIG is not available, standard pooled intravenous immunoglobulin (IVIG) (400 mg/kg given in one dose) can be given. Acyclovir (40–80 mg/kg) for 5 days or the varicella vaccine (if not contraindicated) can also be given as post-exposure prophylaxis within 3 days of exposure. Either of these options offers an efficacy of 70–85% compared to 90% efficacy for VariZIG.

Further information may be obtained by calling the Centers for Disease Control and Prevention's Immunization Information Hotline (800-232-2522).

B. Herpes Zoster

Shingrix, HZ/su (GlaxoSmithKline Biologics), an adjuvanted recombinant subunit vaccine, is approved by the FDA for VZV, and is recommended for individuals 50 years of age and older. *Shingrix is preferred over the older live attenuated VZV vaccine (ZOSTAVAX, see below)*. Shingrix is particularly effective in reducing the incidence of herpes zoster infection and postherpetic neuralgia in adults 70 years of age and older; immunosenescence to the vaccine does not appear to occur in older patients; in fact, strong, persistent immune responses are seen more than 10 years after initial vaccination. It can also be used in immunosuppressed patients. Two doses of the vaccine given 2 months apart had 97% efficacy in preventing herpes zoster. Shingrix also is safe in people living with HIV and with immune restoration (typically CD4 cell counts above 50 cells/mcL), recipients of autologous stem cell transplants, and adults with autoimmune disease taking immunosuppressive therapy.

The older live attenuated VZV vaccine, ZOSTAVAX (19,400 plaque forming units [pfu] of Oka/Merck strain) contains at least 14 times the concentration of varicella virus found in VARIVAX. ZOSTAVAX has been recommended for persons 60 years and older because it reduces the incidence of herpes zoster by 33–55% in the first 3 years after vaccination and reduces the incidence of postherpetic neuralgia by 55–67%. The efficacy of ZOSTAVAX wanes over time, from 69% in the first year after vaccination to 45% by the third year. ZOSTAVAX is safe but only moderately immunogenic among people living with HIV and with a CD4 cell count of at least 200 cells/mcL. Decreased efficacy occurs in patients older than 70, and this vaccine should not be given to immunosuppressed persons. Nonetheless, hematologic oncology patients taking anti-CD20 monoclonal antibodies may be successfully vaccinated with ZOSTAVAX. An increased risk of herpes zoster during a 6-week interval following vaccination is reported among patients taking immunosuppressant medications. This vaccine provides protection for about 3 years.

Even if the person has had a prior episode of herpes zoster, either of the two zoster vaccines has efficacy and can be administered. No specific recommendations exist regarding how long to wait between a zoster outbreak and administering the vaccine; the CDC recommends waiting at least until the outbreak has resolved. Concurrent administration of the adjuvanted recombinant subunit vaccine or the live attenuated VZV vaccine with pneumococcal vaccine is safe. This policy is based on CDC analysis of data, although some experts including original statements of the manufacturer of ZOSTAVAX (Merck & Co.) contend that the two vaccines should be separated by 4 weeks. If a varicella vaccine is mistakenly administered to an adult instead of the adjuvanted recombinant subunit vaccine or the live attenuated zoster vaccine, the dose should be considered invalid and the patient should be administered a dose of zoster vaccine at the same visit. The zoster vaccine cannot be used in children in place of varicella vaccine; if the vaccine is accidentally given to a child, the event should be reported to the CDC.

- Cohen E. Herpes zoster and postherpetic neuralgia. *Clin Infect Dis.* 2020. [Epub ahead of print] [PMID: 32829389]
- Ghanavatian S et al. Premedication with gabapentin significantly reduces the risk of postherpetic neuralgia in patients with neuropathy. *Mayo Clin Proc.* 2019;94:484. [PMID: 30718068]
- Hastie A et al. Immunogenicity of the adjuvanted recombinant zoster vaccine: persistence and anamnestic response to additional doses administered 10 years after primary vaccination. *J Infect Dis.* 2020. [Epub ahead of print] [PMID: 32502272]
- Hayward K et al. Management of herpes zoster (shingles) during pregnancy. *J Obstet Gynaecol.* 2018;38:887. [PMID: 29565203]
- Mangioni D et al. Adjuvant treatment of severe varicella pneumonia with intravenous varicella zoster virus-specific immunoglobulins. *Int J Infect Dis.* 2019;85:70. [PMID: 31132473]
- Steinert I et al. Manifestations of herpes virus infections in the nervous system. *Neurol Clin.* 2018;36:725. [PMID: 30366551]
- Tseng HF et al. The epidemiology of herpes zoster in immunocompetent, unvaccinated adults ≥ 50 years old: incidence, complications, hospitalization, mortality, and recurrence. *J Infect Dis.* 2020;222:798. [PMID: 31830250]
- Wu CY et al. Efficacy of pulsed radiofrequency in herpetic neuralgia: A meta-analysis of randomized controlled trials. *Clin J Pain.* 2020;36:887. [PMID: 32701526]

3. Epstein-Barr Virus & Infectious Mononucleosis



ESSENTIALS OF DIAGNOSIS

- ▶ Malaise, fever, and (exudative) sore throat.
- ▶ Palatal petechiae, lymphadenopathy, splenomegaly; occasionally, a maculopapular rash.
- ▶ Positive heterophile agglutination test (Monospot).
- ▶ Atypical large lymphocytes in blood smear; lymphocytosis.
- ▶ Complications: hepatitis, myocarditis, neuropathy, encephalitis, airway obstruction from adenitis, hemolytic anemia, thrombocytopenia.

► General Considerations

Epstein-Barr virus (EBV, or human herpes virus-4 [HHV-4]) is one of the most ubiquitous human viruses, infecting more than 95% of the adult population worldwide and persisting for the lifetime of the host. Infectious mononucleosis is a common manifestation of EBV and may occur at any age. In the United States the incidence of EBV infection is declining, although prevalence of EBV remains high for those aged 12–19 years. In the developing world, infectious mononucleosis occurs at younger ages and tends to be less symptomatic. Rare cases in older adults occur usually without the full symptomatology. EBV is largely transmitted by saliva but can also be recovered from genital secretions. Saliva may remain infectious during convalescence, for 6 months or longer after symptom onset. The incubation period lasts several weeks (30–50 days). Patients with immunodeficiency disorders are at risk for the full spectrum of EBV-associated disorders.

► Clinical Findings

A. Symptoms and Signs

Fever, sore throat, fatigue, malaise, anorexia, and myalgia typically occur in the early phase of the illness. Physical findings include lymphadenopathy (discrete, nonsuppurative, slightly painful, especially along the posterior cervical chain), transient upper lid edema (Hoagland sign), and splenomegaly (in up to 50% of patients and sometimes massive). A maculopapular or occasionally petechial rash occurs in less than 15% of patients unless ampicillin is given. Conjunctival hemorrhage, exudative pharyngitis, uvular edema, tonsillitis, or gingivitis may occur and soft palatal petechiae may be noted.

Other manifestations include hepatitis, interstitial pneumonitis (sometimes with pleural involvement), cholestasis, gastritis, kidney disease (mostly interstitial nephritis), epiglottitis, and nervous system involvement in 1–5% (mononeuropathies and occasionally aseptic meningitis, encephalitis, cerebellitis, peripheral and optic neuritis, transverse myelitis, or Guillain-Barré syndrome). Vaginal ulcers are rare but may be present. Airway obstruction from lymph node enlargement can occur. Complications of acute disease are more common among older adults.

B. Laboratory Findings

An initial phase of granulocytopenia is followed within 1 week by lymphocytic leukocytosis (greater than 50% of all leukocytes) with atypical lymphocytes (larger than normal mature lymphocytes, staining more darkly, and showing vacuolated, foamy cytoplasm and dark nuclear chromatin) comprising more than 10% of the leukocyte count. Hemolytic anemia, with antibodies, occurs occasionally as does thrombocytopenia (at times marked and life-threatening).

Diagnosis is made based on characteristic manifestations and serologic evidence of infection (the heterophile sheep cell agglutination [**HA**] antibody tests or the correlated mononucleosis spot test [**Monospot**]). These tests usually become positive within 4 weeks after onset of illness and are specific but often not sensitive in early illness. Heterophile antibodies may be absent in young children and in as many as 20% of adults. During acute illness, there is a rise and fall in immunoglobulin M (IgM) antibody to EB virus capsid antigen (VCA) and a rise in immunoglobulin G (IgG) antibody to VCA, which persists for life. Antibodies (IgG) to EBV nuclear antigen (EBNA) appear after 4 weeks of onset and also persist. Absence of IgG and IgM VCA or the presence of IgG EBNA should make one reconsider the diagnosis of acute EBV infection.

PCR for EBV DNA is useful in the evaluation of malignancies associated with EBV. For instance, detection of EBV DNA in CSF shows a sensitivity of 90% and specificity of nearly 100% for the diagnosis of primary CNS lymphoma in patients with AIDS.

► Differential Diagnosis

CMV infection, toxoplasmosis, acute HIV infection, secondary syphilis, HHV-6 infection, rubella, and drug

hypersensitivity reactions may be indistinguishable from infectious mononucleosis due to EBV, but exudative pharyngitis is usually absent and the heterophile antibody tests are negative. With acute HIV infection, rash and mucocutaneous ulceration are common but atypical lymphocytosis is much less common. Heterophile-negative infectious mononucleosis with nonsignificant lymphocytosis (especially if rash or mucocutaneous ulcers are present) should prompt investigation for acute HIV infection. CMV, toxoplasmosis, and, on occasion, EBV can cause heterophile-negative infectious mononucleosis with atypical lymphocytosis. *Mycoplasma* infection may also present as pharyngitis, though lower respiratory symptoms usually predominate. A hypersensitivity syndrome induced by carbamazepine or phenytoin may mimic infectious mononucleosis.

The differential diagnosis of acute exudative pharyngitis includes gonococcal and streptococcal infections, and infections with adenovirus and herpes simplex. Head and neck soft tissue infections (pharyngeal and tonsillar abscesses) may occasionally be mistaken as the lymphadenopathy of mononucleosis.

Complications

Secondary bacterial pharyngitis can occur and is often streptococcal. Splenic rupture (0.5–1%) is a rare but dramatic complication, and a history of preceding trauma can be elicited in 50% of the cases. Acalculous cholecystitis, fulminant hepatitis with massive necrosis, pericarditis, and myocarditis are also infrequent complications.

Treatment

A. General Measures

Over 95% of patients with acute EBV-associated infectious mononucleosis recover without specific antiviral therapy. Treatment is symptomatic with NSAIDs or acetaminophen and warm saline throat irrigations or gargles three or four times daily. Acyclovir decreases viral shedding but shows no clinical benefit. Corticosteroid therapy, although widespread, is not recommended in uncomplicated cases; its use is reserved for impending airway obstruction from enlarged lymph nodes, hemolytic anemia, and severe thrombocytopenia. The value of corticosteroid therapy in impending splenic rupture, pericarditis, myocarditis, and nervous system involvement is less well established. If a throat culture grows beta-hemolytic streptococci, a 10-day course of penicillin or azithromycin is indicated. Ampicillin and amoxicillin are avoided because of the frequent association with rash (90%), although one recent study indicates that the incidence of drug hypersensitivity is much lower than previously reported.

The role of antiviral prophylaxis for preventing posttransplantation EBV infection and sequelae, including posttransplant lymphoproliferative disorders (PTLD) in patients who are donor organ EBV-positive and recipient negative (the main risk factor for both early PTLD [less

than 1 year posttransplantation] and late PTLD [more than 1 year] after transplantation) remains controversial. The 2019 guidelines by the American Society of Transplantation Infectious Disease Community of Practice emphasize the importance of reduction of immunosuppression for PTLD but also note that rituximab and cytotoxic chemotherapy are useful for EBV-positive, CD20-positive lymphoproliferative states.

A 2018 retrospective study indicated that prophylaxis with acyclovir, valacyclovir, ganciclovir, or valganciclovir delayed primary EBV infection at 100 days posttransplant. A decreased incidence of late-onset PTLD and EBV-related neoplasia in treated patients was also noted.

A recent phase 2 clinical trial compared standard of care treatment for EBV-associated lymphomas (R-CHOP) to R-CHOP plus ibrutinib (a Bruton tyrosine kinase inhibitor) and did not show a significant difference in response to treatment or survival. Trials are ongoing to establish the efficacy of autologous T cells targeting latent membrane proteins as adjuvant therapy in EBV-associated lymphomas.

B. Treatment of Complications

Hepatitis, myocarditis, and encephalitis are treated symptomatically. Rupture of the spleen requires splenectomy and is most often caused by deep palpation of the spleen or vigorous activity. *Patients should avoid contact or collision sports for at least 4 weeks to decrease the risk of splenic rupture (even if splenomegaly is not detected by physical examination, which can be insensitive).*

Prognosis & Prevention

In uncomplicated cases, fever disappears in 10 days and lymphadenopathy and splenomegaly in 4 weeks. The debility sometimes lingers for 2–3 months.

Death is uncommon and is usually due to splenic rupture, hypersplenic phenomena (severe hemolytic anemia, thrombocytopenic purpura), or encephalitis.

4. Other EBV-Associated Syndromes

EBV viral antigens are found in more than 90% of patients with endemic (African) Burkitt lymphoma and nasopharyngeal carcinoma (among whom quantified EBV DNA can be used to follow disease). Risk factors for Burkitt lymphoma include a history of malaria (which may decrease resistance to EBV infection), while risk factors for nasopharyngeal carcinoma include long-term heavy cigarette smoking and seropositive EBV serologies (VCA and deoxyribonuclease [DNase]). VCA-IgA in peripheral blood is a sensitive and specific predictor for nasopharyngeal carcinoma in an endemic area.

Among Hodgkin lymphoma patients, EBV seropositivity is common when the disease is found in the developing world or is associated with HIV infection, when pathologic specimens show mixed cellularity, and when patients are younger than 10 years or older than 45 years at onset of the lymphoma. The EBV-seropositive patients have a worse prognosis for early stages of Hodgkin lymphoma.

Chronic EBV infection is associated with aberrant cellular immunity (a low frequency of EBV-specific CD8⁺ T cells), an X-linked lymphoproliferative syndrome (Duncan disease), lymphomatoid granulomatosis, and a fatal T-cell lymphoproliferative disorder in children.

EBV is an important trigger for hemophagocytic lymphohistiocytosis among immunodeficient patients and causes B-cell lymphomas (such as primary CNS lymphoma in people living with HIV), natural killer (NK)/T-cell lymphoma, and posttransplant lymphoproliferative disorders. CD30 and EBV viral loads are prognostic markers for EBV-associated lymphoproliferative disease. PTLD is commonly associated with EBV, especially in children. EBV-naïve patients who receive a donor organ from an EBV-infected donor are at the highest risk for the development of PTLD. EBV serostatus, however, is not associated with overall survival among patients with PTLD. Decreasing the iatrogenic immunosuppression given to prevent graft rejection is the initial step in managing such patients, while rituximab is effective in treating more than two-thirds of cases. Oral mucocutaneous ulcerative disease in people living with HIV may be due to EBV infection.

Age is a major determinant of the type of tumor associated with EBV. T- and NK-cell lymphomas caused by chronic active EBV infections are more frequent in childhood, while peripheral T-cell lymphomas and diffuse large B-cell lymphomas are more common in older patients due to waning immunity. EBV is also associated with leiomyomas in children with AIDS and with nasal T-cell lymphomas.

► When to Admit

Presence of severe complications of EBV disease including the following:

- Acute meningitis, encephalitis, or Guillain-Barré syndrome.
- Severe thrombocytopenia; significant hemolysis.
- Potential splenic rupture.
- Airway obstruction from severe adenitis.
- Pericarditis.
- Abdominal findings mimicking an acute abdomen.

Kerr JR. Epstein-Barr virus (EBV) reactivation and therapeutic inhibitors. *J Clin Pathol*. 2019;72:651. [PMID: 31315893]

Stocker N et al. Pre-emptive rituximab treatment for Epstein-Barr virus reactivation after allogeneic hematopoietic stem cell transplantation is a worthwhile strategy in high-risk recipients: a comparative study for immune recovery and clinical outcomes. *Bone Marrow Transplant*. 2020;55:586. [PMID: 31562397]

Yoon SE et al. A phase II study of ibrutinib in combination with rituximab-cyclophosphamide-doxorubicin hydrochloride-vincristine sulfate-prednisone therapy in Epstein-Barr virus-positive, diffuse large B cell lymphoma (54179060LYM2003: IVORY study): results of the final analysis. *Ann Hematol*. 2020;99:1283. [PMID: 32333154]

5. Cytomegalovirus Disease



ESSENTIALS OF DIAGNOSIS

- ▶ Mononucleosis-like syndrome.
- ▶ Frequent pathogen seen in transplant populations.
- ▶ Diverse clinical syndromes in HIV (retinitis, esophagitis, pneumonia, encephalitis).
- ▶ Most important infectious cause of congenital abnormalities.

► General Considerations

Most CMV infections are asymptomatic. After primary infection, the virus remains latent in most body cells. Seroprevalence in adults of Western developed countries is about 60–80% but is higher in developing countries. The virus can be isolated from a variety of tissues under nonpathogenic conditions. Transmission occurs through sexual contact, breastfeeding, blood products, or transplantation; it may also occur person-to-person (eg, day care centers) or be congenital. Serious disease occurs primarily in immunocompromised persons, including those with inflammatory bowel disease.

There are three recognizable clinical syndromes: (1) perinatal disease and CMV inclusion disease, (2) diseases in immunocompetent persons, and (3) diseases in immunocompromised persons. Congenital CMV infection is the most common congenital infection in developed countries (about 0.6% of live births, with higher rates in underdeveloped areas and among lower socioeconomic groups). Transmission is much higher from mothers with primary disease than those with reactivation (40% vs 0.2–1.8%). About 10% of infected newborns will be symptomatic with CMV inclusion disease.

In immunocompetent persons, acute CMV infection is the most common cause of the mononucleosis-like syndrome with negative heterophile antibodies. In critically ill immunocompetent adults, CMV reactivation is associated with prolonged hospitalization and death. CMV appears to be involved in the malignant manifestations of glioblastoma multiforme.

In immunocompromised persons, solid organ and bone marrow transplant patients are at highest risk for disease from CMV reactivation for a year after allograft transplantation (but especially during the first 100 days posttransplantation) and in particular when graft-versus-host disease is present or when the donor is CMV seropositive and the recipient is seronegative. Depending on the serostatus of the donor and recipient, disease may present as primary infection or reactivation. The risk of CMV disease is proportionate to the degree of immunosuppression and manifestations may differ by the cause. CMV may contribute to transplanted organ dysfunction, which often mimics organ rejection. CMV retinitis may develop after solid organ or bone marrow transplantation. CMV disease in people living with HIV (retinitis, serious gastrointestinal

disease) occurs most prominently when the CD4 cell count is less than 50 cells/ μ mL and can be a marker for increased mortality. Antiretroviral therapy (ART) reduces the frequency of retinitis and may reverse active disease. Patients with immune recovery with CD4 cell count greater than 100 cells/ μ mL show decreased mortality. CMV retinitis associated with intravitreal delivery of corticosteroids (injections or implants) or systemic anti-TNF antibodies is also described. Occasionally, CMV retinitis presents in immunocompetent persons. Serious gastrointestinal CMV disease also occurs after organ transplantation, cancer chemotherapy, or corticosteroid therapy. CMV may exist alongside other pathogens, such as *Cryptosporidium*, in up to 15% of patients with AIDS cholangiopathy. CMV pneumonitis occurs in transplant recipients (mainly bone marrow and lung) with a 60–80% mortality rate and less often in AIDS patients. CMV pneumonitis in hematologic malignancies (eg, lymphoma) is increasingly reported. Neurologic CMV in patients with advanced AIDS is usually associated with disseminated CMV infection.

► Clinical Findings

A. Symptoms and Signs

1. Perinatal disease and CMV inclusion disease—CMV inclusion disease in infected newborns is characterized by hepatitis, thrombocytopenia, microcephaly, periventricular CNS calcifications, mental retardation, and motor disability. Hearing loss develops in more than 50% of infants who are symptomatic at birth, making CMV a leading cause of pediatric hearing loss. Most infected neonates are asymptomatic, but neurologic deficits may ensue later in life, including hearing loss in 15% and cognitive impairment in 10–20%. Perinatal infection acquired through breastfeeding or blood products typically has a benign clinical course.

2. Disease in immunocompetent persons—Acute CMV infection is characterized by fever, malaise, myalgias, arthralgias, and splenomegaly. Unlike in EBV mononucleosis, exudative pharyngitis or cervical lymphadenopathies are uncommon, but cutaneous rashes (including the typical maculopapular rash after exposure to ampicillin) are common. The mean duration of symptoms is 7–8 weeks. Complications include mucosal gastrointestinal damage, encephalitis, severe hepatitis, thrombocytopenia (on occasion, refractory), the Guillain-Barré syndrome, pericarditis, and myocarditis. The risk of Guillain-Barré syndrome developing after primary CMV infection is estimated to be 0.6–2.2 cases per 1000 primary infection, similar to that seen with *Campylobacter jejuni* infection. A mononucleosis-like syndrome due to CMV can also occur post splenectomy, often years later and associated with a protracted fever, marked lymphocytosis, and impaired anti-CMV IgM response.

3. Disease in immunocompromised persons—Distinguishing between CMV infection (with evidence of CMV replication) and CMV disease (evidence for systemic symptoms or organ invasion by pathologic diagnosis) is important. In addition to people living with HIV, those

who have undergone transplantation (solid organ or hematopoietic stem cell) show a wide spectrum of disease including ocular, gastrointestinal (eg, colitis, esophagitis, and acute cholecystitis), kidney, and CNS disease, as outlined above. CMV viremia, assessed with “viral loads,” serve as an important predictor of disease presence.

A. CMV RETINITIS—A funduscopic examination reveals neovascular, proliferative lesions (“pizza-pie” retinopathy). Immune restoration with ART is associated with CMV vitritis and cystoid macular edema.

B. GASTROINTESTINAL AND HEPATOBILIARY CMV—Esophagitis presents with odynophagia. Gastritis can occasionally cause bleeding, and small bowel disease may mimic inflammatory bowel disease or may present as ulceration or perforation. Colonic CMV disease causes diarrhea, hematochezia, abdominal pain, fever, and weight loss and may mimic inflammatory bowel disease. CMV hepatitis commonly complicates liver transplantation and appears to be increased in those with hepatitis B or hepatitis C viral infection.

C. RESPIRATORY CMV—CMV pneumonitis is characterized by cough, dyspnea, and relatively little sputum production. Concomitant infection with *Pneumocystis jirovecii* occurs among patients regardless of HIV status.

D. NEUROLOGIC CMV—Neurologic syndromes associated with CMV include polyradiculopathy, transverse myelitis, ventriculoencephalitis (suspected with ependymitis), and focal encephalitis. These manifestations are more prominent in patients with advanced AIDS in whom the encephalitis has a subacute onset.

B. Laboratory Findings

1. Mothers and newborns—Pregnant women should be tested for CMV viremia every 3 months if found to be seropositive during the first trimester. Congenital CMV disease is confirmed by presence of the virus in amniotic fluid or an IgM assay from fetal blood. Amniocentesis is less reliable before 21 weeks of gestation (due to inadequate fetal urinary development and release into the amniotic fluid), but amniocentesis is attendant with greater risk when performed after 21 weeks of gestation. PCR assays of dried blood samples from newborns, micro-enzyme-linked immunosorbent assay (ELISA), shell-vial culture, or culture of urine, saliva, or blood specimens obtained during the first 3 weeks of life are used to diagnose congenital CMV infection.

2. Immunocompetent persons—The acute mononucleosis-like syndrome is characterized by initial leukopenia; within 1 week, it is followed by absolute lymphocytosis with atypical lymphocytes. Abnormal liver biochemical tests are common in the first 2 weeks of the disease (often 2 weeks after the fever). Detection of CMV DNA, specific IgM, or a fourfold increase of specific IgG levels supports the diagnosis of acute infection.

3. Immunocompromised persons—CMV retinitis is diagnosed on the basis of the characteristic ophthalmoscopic findings. In people living with HIV, negative CMV

serologies lower the possibility of the diagnosis but do not eliminate it. Cultures alone are of little use in diagnosing AIDS-related CMV infections since viral shedding of CMV is common. Detection of CMV by quantitative DNA PCR of the CSF should be used to diagnose CNS infection since cultures are not specific for disease.

Detection of CMV by quantitative DNA PCR is also used in posttransplant patients to guide both treatment and prevention and should be interpreted in the context of clinical and pathologic findings. CMV DNA levels are internationally standardized and have replaced conventional CMV antigenemia tests in many settings. The PCR is sensitive in predicting clinical disease. Serial PCR should be performed and compared using the same specimen type (ie, whole blood or plasma). To assist in the diagnosis of CMV pneumonia, bronchoalveolar lavage fluid can be tested to quantify CMV DNA levels with a viral load assay. Rapid shell-vial cultures detect early CMV antigens with fluorescent antibodies in 24–48 hours. Shell-vial cultures are more useful on bronchoalveolar lavage fluid than in routine blood monitoring. CMV colitis can occur in the absence of a detectable viremia. A new ELISPOT assay is superior to Quantiferon assays in reports from China and may show potential for both diagnosis and following disease in transplant recipients.

C. Imaging

The chest radiographic findings of CMV pneumonitis are consistent with interstitial pneumonia.

D. Biopsy

Tissue confirmation is especially useful in diagnosing CMV pneumonitis and CMV gastrointestinal disease; the diagnosis of colonic CMV disease is made by mucosal biopsy showing characteristic CMV histopathologic findings of intranuclear (“owl’s eye”) and intracytoplasmic inclusions. In situations where histopathologic or immunohistochemical findings are not seen but CMV colitis is suspected, CMV DNA PCR can be used to identify additional cases.

► Treatment & Prognosis

In immunocompetent persons, CMV infection is usually self-limited, and no specific antiviral therapy is needed. In contrast, in immunocompromised persons, treatment of CMV disease is necessary. All types of CMV disease in immunocompromised patients (particularly those with AIDS or post-solid organ transplant) typically are treated initially with intravenous ganciclovir (recommended dose is 5 mg/kg every 12 hours, although this needs to be adjusted for kidney function) until two CMV PCRs 1 week apart are negative (usually 14–21 days). Oral valganciclovir (900 mg every 12 hours), which also needs to be adjusted for kidney function, is an acceptable alternative in patients with non-life-threatening disease.

Pneumonia due to CMV in hematopoietic stem cell transplant recipients is treated even more aggressively, with 5 mg/kg of ganciclovir intravenously every 12 hours for 21 days followed by 5 mg/kg daily for 3–4 weeks plus CMV

immunoglobulin (500 mg/kg) or CMV immunoglobulin (150 mg/kg) twice per week for 2 weeks and then once weekly for an additional 4 weeks.

CMV infections in immunosuppressed patients require a reduction of immunosuppression when possible (especially for muromonab, azathioprine, or mycophenolate mofetil; data are less consistent for alemtuzumab used for graft-versus-host disease and not consistently associated with a risk of CMV disease). Secondary prophylaxis is typically maintained until immune restoration (with two CD4 cell counts greater than 100 cells/mcL present for at least 6 months in the setting of HIV infection). Prolonged prophylaxis may be necessary in other immunosuppressed patients, such as those receiving TNF inhibitors.

Foscarnet and cidofovir are reserved for treatment of resistant infections. Filociclovir (also known as cyclopropavir or MBX-400) is a methylenecyclopropane nucleoside analog currently in phase 2 clinical trials for the treatment of CMV-related disease in transplant patients. Other agents that may be useful in resistant CMV infections include CMV immunoglobulin, maribavir, leflunomide, sirolimus-based therapy, artesunate, and adoptive immunotherapy. Rare cases of post-hematopoietic stem cell transplant CMV meningoencephalitis have been treated successfully using adoptive T cells against CMV.

Treatment of CMV retinitis is discussed in Chapter 7.

► Prevention

Two live vaccines (based on the fibroblast-adapted AD169 and Towne CMV strains, respectively) were shown to be safe and well-tolerated in clinical trials. However, the Towne vaccine was not effective in preventing primary infection or viral reactivation in kidney transplant patients or in seronegative women. A vaccine candidate based on a replication defective AD169 virus (named V160) has been shown to be safe and immunogenic in seronegative adults.

A major source of CMV for pregnant women is their own young children, particularly those in childcare. These women can decrease their risk of contracting primary CMV just before pregnancy or during pregnancy by practicing hand hygiene after changing diapers and after contact with respiratory secretions; avoiding kissing young children on the face; and avoiding sharing utensils, food, and cleansing objects that have been in contact with children’s secretions. CMV serologic tests are being evaluated to diagnose primary maternal CMV infection and are under review for use as a screening tool during the first trimester of pregnancy. Early antiviral therapy with valganciclovir is under study to prevent vertical transmission of CMV.

ART is effective in preventing CMV infections in people living with HIV. Primary prevention is best accomplished by good hand hygiene and use of barrier methods during sexual contacts with persons who are members of high-prevalence groups (ie, men who have sex with men, injection drug users, and those who have exposure to children in childcare).

The use of leukocyte-depleted blood products effectively reduces the incidence of CMV disease in patients who have undergone transplantation. Prophylactic and

preemptive strategies (eg, antiviral agents only when antigen detection or PCR assays show evidence of active CMV replication) appear equally effective in preventing invasive disease and mortality after hematopoietic stem cell transplant. The appropriate management of transplant patients is based on the serostatus of the donor and the recipient. All effective anti-CMV therapies can serve as prophylactic agents for CMV-seropositive transplants or for CMV-seronegative recipients of CMV-positive organ transplants. Starting CMV prophylaxis 7–14 days after transplant may help reduce late-onset CMV end-organ disease. The typical dose for valganciclovir prophylaxis is 450 mg orally twice daily, although a 2018 prospective trial in kidney transplant recipients indicated that prophylaxis with low-dose valganciclovir (450 mg/day, three times a week for 6 months) seemed to be effective. Acyclovir may also be used. Letermovir is useful in prophylaxis against CMV infections in adult allogenic hematopoietic stem cell transplant recipients. It is given as 480 mg orally daily with dose adjustments for cyclosporine administration and for advanced kidney dysfunction (less than a creatinine clearance of 10 mL/min). Major side effects reported to date include cough, diarrhea, headache, nausea, stomach pain, weakness, and vomiting. Recommended duration of CMV prophylaxis in posttransplant patients and in other immunocompromised patients varies by the type of transplant.

CMV immune globulin may also be useful in reducing the incidence of bronchiolitis obliterans in the bone marrow transplant population and is used in some centers as part of the prophylaxis in kidney, liver, and lung transplantation patients. CMV immune globulin as prophylaxis is not recommended in hematopoietic stem cell transplant recipients.

► When to Refer

- People with AIDS with retinitis, esophagitis, colitis, hepatobiliary disease, or encephalitis.
- Organ and hematopoietic stem cell transplants with suspected reactivation CMV.

► When to Admit

- Escalating CMV viral load at the onset of illness.
- Risk of colonic perforation.
- Evaluation of unexplained, advancing encephalopathy.
- Initiation of treatment with intravenous anti-CMV agents.

Alonso L. Successful treatment of post-transplant CMV meningoencephalitis with third-party CMV virus-specific T cells: lessons learned. *Pediatr Transplant*. 2019;e13584. [PMID: 31556188]

Hussein ITM et al. The discovery and development of filociclovir for the prevention and treatment of human cytomegalovirus-related disease. *Antiviral Res*. 2020;176:104710. [PMID: 31940473]

Plotkin SA et al. Vaccination against the human cytomegalovirus. *Vaccine*. 2019;37:7437. [PMID: 29622379]

Shahar-Nissan K et al. Valaciclovir to prevent vertical transmission of cytomegalovirus after maternal primary infection during pregnancy: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2020;396:779. [PMID: 32919517]

US Department of Health and Human Services (HHS). AIDSinfo. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV. Cytomegalovirus. 2019 Jun 26:K1-15. https://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_o1.pdf

6. Human Herpesviruses 6, 7, & 8

HHV-6 is a B-cell lymphotropic virus that is the principal cause of **exanthema subitum** (roseola infantum, sixth disease). Primary HHV-6 infection occurs most commonly in children under 2 years of age and is a major cause of infantile febrile seizures (21% in one recent series). HHV-6 is also associated with encephalitis (symptoms may include insomnia, seizures, and hallucinations), autoimmune (Hashimoto) thyroiditis, myocarditis, and acute liver failure. Primary infection in immunocompetent adults is not common but can produce a mononucleosis-like illness. The lymphadenitis may be confused with lymphoma. Pathologically, HHV-6 is associated with mesial temporal sclerosis, which may lead to mesial temporal lobe epilepsy, and HHV-6 is associated with epilepsy syndromes. Reactivation of HHV-6 in immunocompetent adults is rare and can present as encephalitis. Imaging studies in HHV-6 encephalitis typically show lesions in the hippocampus, amygdala, and limbic structures.

Infection during pregnancy and congenital transmission is recognized. Most cases of reactivation occur in immunocompromised persons. Reactivation is associated with graft rejection, graft-versus-host disease, and bone marrow suppression in transplant patients and with encephalitis and pneumonitis in AIDS patients. In recipients of hematopoietic stem cell transplants, HHV-6 may cause fever. It is also associated with an HHV-6-induced encephalitis (diagnosed with multiplex PCR assays) that is correlated strongly with umbilical cord hematopoietic cell transplants (although HHV-6 is not associated with survival in such patients and surveillance for the virus may not be needed).

HHV-6 is on occasion also associated with drug-induced hypersensitivity syndromes. HHV-6 may cause fulminant hepatic failure and acute decompensation of chronic liver disease in children. Purpura fulminans and corneal inflammation are reported. Two variants (A and B) of HHV-6 have been identified. HHV-6B is the predominant strain found in both normal and immunocompromised persons. Ganciclovir, cidofovir, and foscarnet (but not acyclovir) appear to be clinically active against HHV-6. Adoptively transferred virus-specific T-cell therapy is also being developed for treatment of HHV-6 and other viral infections in hematopoietic stem cell transplant recipients.

HHV-7 is a T-cell lymphotropic virus that is associated with roseola seizures and, rarely, encephalitis, even in immunocompetent adults. Pregnant women are often infected. Infection with HHV-7 is synergistic with CMV in kidney transplant recipients.

HHV-8 (see also Chapter 31) is associated with Kaposi sarcoma, multicentric Castleman disease, and primary effusion (body cavity) lymphoma. HHV-8 infection is endemic in Africa; transmission seems to be primarily horizontal in childhood from intrafamilial contacts and continues through adulthood possibly by nonsexual routes.

Balakrishna JP et al. Human herpes virus 6 (HHV6)-associated lymphadenitis: pitfalls in diagnosis in benign and malignant settings. *Am J Surg Pathol.* 2018;42:1402. [PMID: 29975251]
Bartolini L et al. Infection with HHV-6 and its role in epilepsy. *Epilepsy Res.* 2019;153:34. [PMID: 30953871]

Eliassen E et al. HHV-6-associated neurological disease in children: epidemiologic, clinical, diagnostic, and treatment considerations. *Pediatr Neurol.* 2020;105:10. [PMID: 31932119]

MAJOR VACCINE-PREVENTABLE VIRAL INFECTIONS

1. Measles

ESSENTIALS OF DIAGNOSIS

- ▶ Onset of prodrome 7–18 days after exposure in an unvaccinated patient.
- ▶ Prodrome: fever, coryza, cough, conjunctivitis, malaise, irritability, photophobia, Koplik spots.
- ▶ Rash: brick red, maculopapular; appears 3–4 days after onset of prodrome; begins on the face and proceeds “downward and outward,” affecting the palms and soles last.
- ▶ Leukopenia.

General Considerations

Measles is a reportable acute systemic paramyxoviral infection transmitted by direct contact with infectious droplets or by airborne spread. It is highly contagious with communicability greatest during the preeruptive and catarrhal stages but continues 4 days after the appearance of rash. Measles elimination is defined as the absence of endemic measles virus transmission in an area for 12 months or longer. Measles remains a major cause of mortality with more than 140,000 estimated deaths globally in 2018, mostly in children younger than 5 years old.

As of April 2019, preliminary data from the World Health Organization (WHO) indicate that reported measles cases rose by 300% in the first 3 months of 2019, compared to the same period in 2018. The WHO previously considered measles eradicated in most countries worldwide, including the Americas. Many countries, however, are reporting ongoing measles outbreaks, including the Democratic Republic of the Congo, Nigeria, Guinea, Chad, Burundi, Madagascar, Central African Republic, Ethiopia, Philippines, Mexico, Yemen, Sudan, Ukraine, Brazil, Kazakhstan, Uzbekistan, India, and Bangladesh. During 2019, measles outbreaks occurred in countries with high

vaccination coverage, including the United States, Israel, Thailand, Tunisia, New Zealand, and many European countries and the Pacific Islands. As of October 7, 2020, the WHO European Region reported a total of 12,028 measles cases. This is compared to 104,554 cases and 42 deaths in 2019.

Most measles cases in the United States are due to either travel to endemic areas or exposure to individuals who have not been vaccinated against measles. Intentional undervaccination continues to undermine measles elimination programs, and many measles vaccination campaigns have been halted by COVID-19.

► Clinical Findings

A. Symptoms and Signs

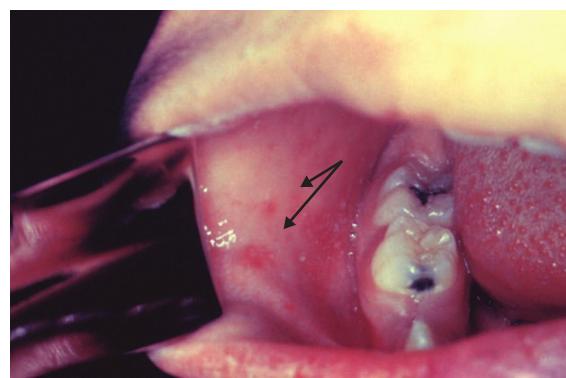
The incubation period for measles is 10–14 days. The illness starts with a prodromal phase manifested by high-grade fever (often as high as 40–40.6°C), malaise, coryza (nasal obstruction, sneezing, and sore throat resembling upper respiratory infections), persistent cough, and conjunctivitis (redness, swelling, photophobia, and discharge). These symptoms intensify over 2–4 days before onset of the rash and peak on the first day of the rash. The fever persists through the early rash (about 5–7 days) (Table 32–2).

The characteristic measles rash appears on the face and behind the ears. Initial lesions are pinhead-sized papules that coalesce to form a brick red, irregular, blotchy maculopapular rash. The rash spreads to the trunk and extremities, including the palms and soles. It lasts for 3–7 days and fades in the same manner it appeared. Other findings include pharyngeal erythema, tonsillar exudate, moderate generalized lymphadenopathy, and, at times, splenomegaly.

Koplik spots (small, irregular, and red with whitish center on the mucous membranes) are pathognomonic of measles (Figure 32–4). They appear about 2 days before the rash and last 1–4 days as tiny “table salt crystals” on the palatal or buccal mucosa opposite the molars.

B. Laboratory Findings

Leukopenia is usually present unless secondary bacterial complications exist. A lymphocyte count under 2000/mcL



▲ **Figure 32–4.** Very small, bright red spots on the buccal mucosa indicative of Koplik spots. (Public Health Image Library, CDC.)

($2.0 \times 10^9/L$) is a poor prognostic sign. Thrombocytopenia is common. Proteinuria is often observed.

Detection of IgM measles antibodies with ELISA or a fourfold rise in serum hemagglutination inhibition antibody supports the diagnosis. IgM assays can be falsely negative the first few days of infection and falsely positive in the presence of rheumatoid factor or with acute rubella, erythrovirus (formerly parvovirus B19), or HHV-6 infection.

Measles virus is technically difficult to culture. Real-time reverse transcriptase-PCR (RT-PCR), available from the CDC and some public health laboratories, can help establish a diagnosis promptly.

► Differential Diagnosis

Measles is usually diagnosed clinically but may be mistaken for Kawasaki disease and other exanthematous infections (Table 32–2). Frequent difficulty in establishing a diagnosis suggests that measles may be more prevalent than is recognized.

► Complications

A. Respiratory Tract Disease

Early in the course of the disease, bronchopneumonia or bronchiolitis due to the measles virus may occur in up to 5% of patients and result in serious respiratory difficulties. Bronchiectasis may occur in up to a quarter of nonvaccinated children. The incidence of severe respiratory disease may be increased among immunocompromised children and pregnant women.

B. Central Nervous System

Postinfectious encephalomyelitis occurs in 0.05–0.1% of cases, with higher rates occurring in adolescents. It is an acute demyelinating disease that usually starts 3–7 days after the rash. Seizures, coma, and other neurologic symptoms and signs may develop. Treatment is symptomatic and supportive. Virus isolation from the CNS is uncommon. There is an appreciable mortality (10–20%) and morbidity (33% of survivors are left with neurologic deficits).

Measles inclusion body encephalitis is another form of neurologic complication that results in neurologic deterioration and death within months of the acute illness among patients with impaired cellular immunity. Treatment is supportive, including stopping immunosuppressants when feasible. Interferon and ribavirin are variably successful.

Subacute sclerosing panencephalitis is a very rare, fatal CNS complication that occurs 5–15 years after infection. It is characterized by progressive deterioration of motor and cognitive function leading to death. It is more common in boys of rural backgrounds who are infected with measles before 2 years of age.

C. Other Complications

Immediately following measles, secondary bacterial infection, particularly otitis media (the most common complication), cervical adenitis, and pneumonia, occurs in about

15% of patients. Keratoconjunctivitis is a serious complication that caused blindness before the widespread use of measles vaccine and vitamin A supplementation. Diarrhea and protein-losing enteropathy (prodromal rectal Koplik spots may occur) are significant complications among malnourished children, although the mortality associated with diarrhea is primarily 1 week prior to and 4 weeks after the measles rash, with no longer-term mortality shown with measles-associated diarrhea. Some data implicate the measles virus in the pathogenesis of rheumatoid arthritis.

► Treatment

Treatment is symptomatic, including antipyretics and fluids as needed. Vitamin A supplementation for children reduces pediatric morbidity and measles-associated mortality. Data are less substantial for adult supplementation, although many advocate megadose vitamin A given to the mother at the time of delivery in order to boost infant levels of the vitamin.

Measles virus is susceptible to ribavirin and other antivirals in vitro. Ribavirin is used in selected severe cases of pneumonitis, but insufficient data prevent recommending antiviral use. Zinc has a role in the maintenance of normal immune functions, but routine zinc supplementation to children with measles is not recommended, again for lack of data.

► Prognosis

It is estimated that 23.2 million deaths were prevented between 2000 and 2018 by use of measles vaccination. In the United States, the case fatality rate is around 2 per 1000 reported cases, with deaths principally due to respiratory and neurologic complications. Deaths in the developing world are mainly related to acute diarrhea and protein-losing enteropathy. Pregnant women with measles may be at increased risk for death. Historically famines are particularly associated with high measles mortality.

► Prevention

The measles vaccine is a live vaccine that is available worldwide as part of the trivalent MMR vaccine or the quadrivalent MMRV vaccine. Because measles is highly contagious, the vaccine coverage rates must exceed 95% to prevent outbreaks. Illness confers permanent immunity. One vaccine dose is about 93% effective. Two doses of vaccine are estimated to be 97% protective. In the United States, based on the National Immunization Survey, 91.5% of children aged 19–35 months received one or more doses of MMR in 2017 and 91.9% of adolescents aged 13–17 years received two or more doses of MMR in 2018. These data suggest considerable geographic disparity. Clustering of unvaccinated individuals increases the likelihood of an outbreak.

At 6 months of age, more than 99% of infants of vaccinated women and 95% of infants of naturally immune women lose maternal antibodies. The susceptibility to measles is 2.4-fold higher if the vaccine is given prior to 15 months (with impact of waning maternal antibody levels). In the United States, children receive their first

vaccine dose of MMR vaccine at 12–15 months of age (<https://www.cdc.gov/vaccines/schedules/hcp/imz-child-adolescent.html>). The second dose is given at age 4–6 years, prior to school entry.

Older children, teens, and adults without evidence of immunity should receive two MMR doses separated by 28 days. For individuals born before 1957, herd immunity is assumed. Persons at high risk for measles exposure (teachers, health care workers, post-high school students, travelers to developing countries) should also receive two vaccination doses at least 28 days apart. Immigrants and refugees should be screened and vaccinated if necessary. The MMRV vaccines may be used in place of the traditional MMR vaccine.

MMR and MMRV vaccine should not be administered to pregnant women, patients with anaphylactic reactions to neomycin, and patients with known primary or acquired immunodeficiency. Asymptomatic patients living with HIV infection with CD4 cell counts higher than 200 cells/mcL should receive the MMR vaccine but not the MMRV vaccine.

Repeated studies *fail to show* an association between vaccination and autism. MMR vaccine can cause fever and transient rash. Severe allergic reactions are rare. Quadrivalent MMRV vaccine is associated with an increased risk of febrile seizures that appears to be age-related; the risk is highest when MMRV is given to infants between 12 and 23 months of age. Postimmunization seizures appear in whole genome studies to be associated with an interferon receptor and a measles receptor. Immune thrombocytopenia is a documented side effect. Rare cases of postimmunization encephalitis are reported.

In case of an outbreak, when susceptible individuals are exposed to measles, MMR vaccine can prevent disease if given within 3 days of exposure. Immunoglobulin should be administered within 6 days of exposure in any high-risk person exposed to measles, followed by active immunization 3 months later. All infants less than 1 year of age should receive intramuscular immunoglobulin (0.5 mL/kg, maximum dose 15 mL). For infants between 6 months and 12 months, MMR vaccination with repeat at 15 months can be given in place of intramuscular immunoglobulin. Pregnant women and severely immunocompromised persons who are exposed to active measles cases should receive IVIG (400 mg/kg).

Patients with measles should be isolated for 4 days after the onset of rash. In the hospital setting, patients with measles should be placed under airborne precautions.

An aerosolized measles vaccine was developed and used in Mexico; however, in 2013, it was found to be inferior to the subcutaneous vaccine. Future vaccines for a variety of infectious agents may utilize measles vectors, thereby augmenting immunity to measles.

► When to Admit

- Meningitis, encephalitis, or myelitis.
- Severe pneumonia.
- Diarrhea that significantly compromises fluid or electrolyte status.

Hviid A et al. Measles, mumps, rubella vaccination and autism: a nationwide cohort study. *Ann Intern Med.* 2019;170:513. [PMID: 30831578]

Di Pietrantonio C et al. Vaccines for measles, mumps, rubella, and varicella in children. *Cochrane Database Syst Rev.* 2020;4: CD004407. [PMID: 32309885]

Patel M et al. National update on measles cases and outbreaks—United States, January 1–October 1, 2019. *MMWR Morb Mortal Wkly Rep.* 2019;68:893. [PMID: 31600181]

Walker TY et al. National, regional, state, and selected local area vaccination coverage among adolescents aged 13–17 years—United States, 2018. *MMWR Morb Mortal Wkly Rep.* 2019;68:718. [PMID: 31437143]

2. Mumps



- Exposure 12–25 days before onset.
- Painful, swollen salivary glands, usually parotid.
- Frequent involvement of testes, pancreas, and meninges in unvaccinated individuals.
- Mumps can occur in appropriately vaccinated persons in highly vaccinated communities.

► General Considerations

Mumps is a paramyxoviral disease spread by respiratory droplets. Children are most commonly affected; however, in outbreaks, infection can affect patients in their second or third decades of life. Mumps can spread rapidly in congregate settings, such as colleges and schools. The incubation period is 12–25 days (average, 16–18 days). The mumps virus spreads through direct contact with respiratory secretions or saliva or infected surfaces. Transmission can also be airborne or via droplets. Up to one-third of affected individuals have subclinical infection, which is still transmissible. Since the MMR vaccine was introduced in 1989, the mumps case rate has decreased by more than 99%, with only a few hundred cases reported most years. Unfortunately, the mumps case rate started to increase in late 2015. From January 2016 to June 2017, 9200 cases were reported, including a large outbreak of close to 3000 cases in one Arkansas community. Between January 1 and September 13, 2019, 47 states and the District of Columbia in the United States reported 2363 mumps cases. From January 1 to January 25, 2020, preliminary data reported to the CDC showed 70 cases in 16 states. A combination of factors contributes to outbreaks, including efficacy of vaccines; waning individual immunity; and crowded conditions, which promote transmission.

► When to Refer

- Any suspect cases should be reported to public health authorities.
- HIV infection.
- Pregnancy.



▲ **Figure 32–5.** Mumps. (Public Health Image Library, CDC.)

► Clinical Findings

A. Symptoms and Signs

Mumps is more serious in adults than in children and appears to occur more commonly in males. *Parotid tenderness and overlying facial edema* (Figure 32–5) are the most common physical findings and typically develop within 48 hours of the prodromal symptoms. Usually, one parotid gland enlarges before the other, but unilateral parotitis occurs in 25% of patients. The parotid duct (orifice of Stensen) may be red and swollen. Trismus may result from parotitis. The parotid glands return to normal within 1 week. Involvement of other salivary glands (submaxillary and sublingual) occurs in 10% of cases. Fever and malaise are variable but often minimal in young children. The entire course of mumps rarely exceeds 2 weeks.

The testes are the most common extra salivary disease site in adults. High fever, testicular swelling, and tenderness (unilateral in 75% of cases) denote orchitis, which usually develops 7–10 days after the onset of parotitis. In the mumps outbreaks that occurred between 2006 and 2010 in the United States, complications from mumps were rare; 3.3–10% of adolescent and adult males developed orchitis (which occurred less frequently in persons who have received two doses of vaccine). Lower abdominal pain and ovarian enlargement suggest oophoritis, which is usually unilateral and occurs in less than 1% of postpubertal women.

Other rare complications, occurring in less than 1% of cases, are meningitis, encephalitis, Guillain-Barré syndrome, hearing loss, priapism or testicular infarction from orchitis, pancreatitis, thyroiditis, keratitis, neuritis, hepatitis, myocarditis, thrombocytopenia, migratory arthralgias, and nephritis. No mumps-related deaths have occurred in the United States in recent outbreaks. A rare cause of mumps is iodine exposure in medical procedures (“iodide mumps”).

B. Laboratory Findings

Mild leukopenia with relative lymphocytosis may be present. Elevated serum amylase usually reflects salivary gland involvement rather than pancreatitis. Mild kidney injury is found in up to 60% of patients.

The characteristic clinical picture usually suffices for diagnosis. An elevated serum IgM is considered diagnostic. Repeat testing 2–3 weeks after the onset of symptoms is recommended if the first assay is negative because the rise in IgM may be delayed, especially in vaccinated persons. A fourfold rise in complement-fixing antibodies to mumps virus in paired serum IgG also confirms infection. Anti-mumps IgM and IgG in the CSF can confirm the diagnosis of mumps-associated meningitis. Nucleic acid amplification techniques, such as RT-PCR, are more sensitive than viral cultures and are available from some commercial laboratories, selected state laboratories, and the CDC. Diagnostic yield is highest if collected during the first 3 days of illness. Confirmatory diagnosis of mumps is also made by isolating the virus preferably from a swab of the duct of the parotid or other affected salivary gland. The virus can also be isolated from CSF early in aseptic meningitis. Vaccinated persons may shed virus for shorter periods of time compared to those who are unvaccinated.

► Differential Diagnosis

Swelling of the parotid gland may be due to calculi in the parotid ducts, tumors, or cysts. Other causes include sarcoidosis, cirrhosis, diabetes, bulimia, pilocarpine usage, and Sjögren syndrome. Parotitis may be produced by pyogenic organisms (eg, *S aureus*, gram-negative organisms [particularly in debilitated individuals with poor oral intake]), drug reaction (phenothiazines, propylthiouracil), and other viruses (HIV, influenza A, parainfluenza, EBV infection, coxsackieviruses, adenoviruses, HHV-6). Swelling of the parotid gland must be differentiated from inflammation of the lymph nodes located more posteriorly and inferiorly than the parotid gland.

► Treatment

Treatment is symptomatic. Topical compresses may relieve parotid discomfort. Some clinicians advocate IVIG for complicated disease (eg, thrombocytopenia), although its definitive role is unproven. No specific treatment exists for orchitis.

► Prevention

Vaccination is the most effective way to prevent mumps.

The vaccination schedule, indications, and contraindications are described in the measles section. The mumps vaccine component of the MMR is less effective than the measles and rubella components. One dose is 78% (range: 49–92%) protective. Two doses of the vaccine are 88% (range: 66–95%) effective. Rare reported complications of mumps vaccination include immune thrombocytopenic purpura and aseptic meningitis.

A 2017 study, evaluating the effect of a third dose of MMR vaccine after a mumps outbreak, showed that the attack rate was significantly lower among students who received a third dose compared with two doses, especially if the second dose was given more than 13 years prior to the outbreak. The CDC recommends a third dose of vaccine in case of an outbreak.

Suspected cases should be isolated. For outbreak control, the most important step is to vaccinate all susceptible individuals. The MMR vaccine is not effective in preventing the disease in unvaccinated patients who already have been exposed to the virus. In the health care setting, the following steps should be taken: implement droplet and standard precautions, isolate patients until swelling subsides (about 9 days from onset), and provide vaccination to health care workers with no evidence of immunity.

► When to Refer

Any suspect cases should be reported to public health authorities.

► When to Admit

- Trismus; meningitis; encephalitis; myocarditis; pancreatitis.
- Severe testicular pain; priapism.
- Severe thrombocytopenia.

Bockelman C et al. Mumps: an emergency medicine-focused update. *J Emerg Med*. 2018;54:207. [PMID: 29110978]

Kaaik P et al. A third dose of measles-mumps-rubella vaccine to improve immunity against mumps in young adults. *J Infect Dis*. 2020;221:902. [PMID: 31112277]

Marin M et al. Recommendation of the Advisory Committee on Immunization Practices for use of a third dose of mumps virus-containing vaccine in persons at increased risk for mumps during an outbreak. *MMWR Morb Mortal Wkly Rep*. 2018;67:33. [PMID: 29324728]

Perez-Vilar S et al; WHO Global Vaccine Safety-Multi Country Collaboration. Enhancing global vaccine pharmacovigilance: proof-of-concept study on aseptic meningitis and immune thrombocytopenic purpura following measles-mumps containing vaccination. *Vaccine*. 2018;36:347. [PMID: 28558983]

3. Rubella

ESSENTIALS OF DIAGNOSIS

- Exposure 14–21 days before onset.
- No prodrome in children, mild prodrome in adults; mild symptoms (fever, malaise, coryza) coincide with, or precede by up to 5 days, the eruption of rash.
- Posterior cervical and postauricular lymphadenopathy 5–10 days before rash.
- Fine maculopapular rash of 3 days' duration; face to trunk to extremities.
- Leukopenia, thrombocytopenia.

► General Considerations

Rubella is a systemic disease caused by a togavirus transmitted by inhalation of infective droplets. It is moderately communicable. Infection usually confers permanent immunity. The incubation period is 14–21 days. The disease is transmissible from 1 week before the rash appears until 15 days afterward.

The last cases of endemic rubella and congenital rubella syndrome were reported in 2009 from the Americas region. Each year in the United States, fewer than 10 cases of rubella are reported, all of which are due to the arrival of infected persons from other countries. In 2015, the WHO declared that the Americas were the first region to be free of rubella and congenital rubella syndrome. Some European countries are facing a challenge with lower immunization coverage among refugees and migrants. Worldwide, cases are decreasing due to widespread implementation of rubella-containing vaccines; as of 2018, the vaccine was added to the national vaccine schedule in 168 of 194 (87%) countries, though it is important to note that extensive variation in the rate of national coverage exists. On the other hand, the number of cases of congenital rubella syndrome remains high, particularly in Africa and Southeast Asia. The increase in congenital rubella syndrome may be secondary to an increase in surveillance and reporting of congenital rubella cases. The WHO set a goal to eliminate rubella in at least five of the six regions (all but the Western Pacific region, which includes China) by 2020, although progress is hampered by lack of resources.

► Clinical Findings

A. Postnatal Rubella

Rubella is a common childhood disease; the majority of the cases are asymptomatic. The clinical picture of rubella is difficult to distinguish from other viral illnesses, such as infectious mononucleosis, measles, echovirus infections, and coxsackievirus infections. Fever and malaise, usually mild, accompanied by tender suboccipital adenitis, may precede the eruption by 1 week. Early posterior cervical and postauricular lymphadenopathy is common. A fine, pink maculopapular rash appears and fades from the face, trunk, and extremities in rapid progression (2–3 days), usually lasting 1 day in each area (Table 32–2).

B. Congenital Rubella

The principal importance of rubella lies in its devastating effects on the fetus in utero causing fetal death, preterm delivery, and teratogenic effects. The severity of symptoms is directly related to the gestational age; fetal infection during the first trimester leads to congenital rubella in at least 80% of fetuses; however, an infection during the fourth month can lead to 10% risk of a single congenital defect. In the second trimester of pregnancy, deafness is the primary complication.

C. Laboratory Findings

When rubella is suspected, the diagnosis requires serologic confirmation. Diagnosis of acute rubella infection is based on elevated IgM antibody, fourfold or greater rise in IgG antibody

titors, or isolation of the virus. Serosensitivity to rubella is thought to change with subsequent pregnancies, although data from Hong Kong (lower immunity) and the United Kingdom (higher immunity) differed in their findings.

IgM is detectable in 50% of persons on day 1 of the rash but in most on day 5 after rash onset. Antibody testing can be performed on sera or saliva. An isolated IgM-positive test does not necessarily imply acute infection. IgM antibodies can persist after an infection or could be false-positive due to cross-reactivity with other antigens such as EBV, CMV, erythrovirus, and rheumatoid factor. This distinction is very important to make when infection is suspected in pregnancy. High-avidity anti-rubella IgG assays can distinguish between recent and remote infection. Low-avidity IgG is observed in acute rubella infections and lasts up to 3 months postinfection. After 3 months, low-avidity antibodies are replaced by high-avidity antibodies indicating remote infection.

The CDC can test for virus by RT-PCR from throat swabs, oral fluids, or nasopharyngeal secretions. The timing of sample collection is important and is best if collected within the first 3 days of an acute illness and within 3 months in case of congenital rubella syndrome. After 3 months of age, up to 50% of infants with congenital rubella syndrome will not shed the virus.

Complications

Complications of rubella are rare aside from the congenital rubella syndrome. Polyarticular arthritis and arthralgia occur more commonly in adult women; involve the fingers, wrists, and knees; and usually subside within 7 days but may persist for weeks. Hemorrhagic manifestations due to thrombocytopenia and vascular damage occur more commonly in children, unlike other complications. Hepatitis has been reported. Encephalitis, another rare complication, occurs more commonly in adults and has a high mortality rate.

Treatment

Rubella infection, including complications, is treated symptomatically.

Prevention

Patients with rubella should be isolated for 7 days after rash onset.

In the United States, monovalent rubella vaccine is not produced. Live attenuated rubella virus vaccine is included in the MMR or MMRV vaccine. It is recommended that the first dose be given between 12 months and 15 months. The second dose is given between age 4 and 6 years, prior to school entry. More details on scheduling, side effects, and contraindications are explained in the measles section. It is important that girls are immune to rubella prior to menarche. In the United States, about 80% of 20-year-old women are immune to rubella.

Rubella vaccine is safe and highly efficacious; a single dose of MMR vaccine is about 97% effective at preventing rubella.

The immune status of pregnant women should be evaluated because antibody titers fall in about 10% of vaccinated individuals within 12 years of vaccination. While no evidence exists for adverse outcomes with MMR immunization of pregnant women, it is still recommended that

women avoid pregnancy for at least 3 months after vaccination. Opportunities should be made available to vaccinate all women of childbearing age.

The administration of live vaccines to immunocompromised patients is controversial. In patients receiving immunosuppressive therapy as well as in patients who have undergone solid organ or bone marrow transplantation, seroconversion is higher to rubella compared with measles, mumps, and varicella. In addition, response to live attenuated vaccines may be lessened due to presence of antibodies from IVIG or other blood products. Safety is another concern when administering live attenuated vaccines to immunocompromised patients. Because MMR vaccine is contraindicated in solid organ transplant recipients, current evidence recommends that seronegative patients receive one or two doses of the MMR vaccine at least 4 weeks prior to solid organ transplantation. Patients who have undergone bone marrow transplant lose antigen-specific antibodies and should be revaccinated regardless of their vaccination history. The revised guidelines recommend MMR and varicella vaccines be given to seronegative patients without graft-versus-host disease 2 years after hematopoietic stem cell transplantation.

Prognosis

Rubella typically is a mild illness and rarely lasts more than 3–4 days. Congenital rubella has a high fetal mortality rate, and the associated congenital defects are largely permanent.

When to Refer

- Pregnancy.
- Meningitis/encephalitis.
- Significant vaccination reactions.
- Any suspect cases should be reported to public health authorities.

Grant GB et al. Progress toward rubella and congenital rubella syndrome control and elimination—worldwide, 2000–2018. MMWR Morb Mortal Wkly Rep. 2019;68:855. [PMID: 31581161]

Hinman AR. Measles and rubella eradication. Vaccine. 2018;36:1. [PMID: 29183733]

World Health Organization. Rubella (CRS) reported cases: WHO vaccine-preventable diseases: monitoring system 2018 global summary. Updated 2019 Jul 15. http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tsincidencecrs.html

4. Poliomyelitis

ESSENTIALS OF DIAGNOSIS

- Incubation period 7–14 days after exposure.
- Headache, stiff neck, fever, vomiting, sore throat.
- Lower motor neuron lesion (flaccid myelitis) with decreased deep tendon reflexes and muscle wasting; sensation intact.

► General Considerations

Poliomyelitis virus, an enterovirus, is highly contagious through fecal-oral route, especially during the first week of infection. There are three wild poliovirus serotypes; however, only wild poliovirus type 1 has remained endemic since 2012. Pakistan and Afghanistan currently are the only countries with endemic wild type poliovirus transmission. Unfortunately, there has been a concerning uptick in the numbers of both wild and vaccine-derived polio cases. In 2019, 29 cases of wild type polio were reported from Afghanistan and 146 from Pakistan. By late 2020, 37 cases of wild type polio were reported from Afghanistan and 65 cases from Pakistan. In 2019, a total of 354 vaccine-derived polio cases were reported from 17 countries, derived mostly from type 2 attenuated live oral poliovirus vaccine (OPV). By late 2020, 302 cases of vaccine-derived polio were reported from 17 countries.

Cases of acute flaccid myelitis (formerly acute flaccid paralysis) resembling polio but not due to poliomyelitis virus are being reported (see Acute Flaccid Myelitis, below).

► Clinical Findings

A. Symptoms and Signs

At least 95% of infections are asymptomatic. Patients who become symptomatic can present with abortive poliomyelitis, nonparalytic poliomyelitis, or paralytic poliomyelitis. Post-poliomyelitis syndrome is the constellation of symptoms that affect polio survivors and is not infectious.

1. Abortive poliomyelitis—Nonspecific symptoms of this minor illness include fever, headache, vomiting, diarrhea, constipation, and sore throat lasting 2–3 days.

2. Nonparalytic poliomyelitis—In addition to the above symptoms, signs of meningeal irritation and muscle spasm occur in the absence of frank paralysis.

3. Paralytic poliomyelitis—Characterized as a flaccid asymmetric paralysis affecting mostly the proximal muscles of the lower extremities; the febrile period is present over 2–3 days. Sensory loss is very rare. Paralytic poliomyelitis is divided into two forms, which may coexist: (1) **spinal poliomyelitis** involving the muscles innervated by the spinal nerves, and (2) **bulbar poliomyelitis** involving the muscles supplied by the cranial nerves (especially nerves IX and X) and of the respiratory and vasmotor centers. The most life-threatening aspect of bulbar poliomyelitis is respiratory paralysis. The incidence of paralytic poliomyelitis is higher when infections are acquired later in life.

4. Post-poliomyelitis syndrome—The syndrome presents with signs of chronic and new denervation. The most frequent symptoms are progressive muscle limb paresis with muscle atrophy, with fasciculations and fibrillation during rest activity. The restless leg syndrome is also reported.

B. Laboratory Findings

The virus may be recovered from throat washings (early) and stools (early and late) and PCR of washings, stool, or

CSF can also facilitate diagnosis. CSF findings include the following: (1) normal or slightly increased pressure and protein, (2) glucose is not decreased, and (3) white blood cells usually number less than 500/mcL ($0.5 \times 10^9/L$) and are principally lymphocytes after the first 24 hours. CSF findings are normal in 5% of patients. Neutralizing and complement-fixing antibodies appear during the first or second week of illness. Serologic testing cannot distinguish between wild type and vaccine-related virus infections.

► Differential Diagnosis

Acute inflammatory polyneuritis (Guillain-Barré syndrome), Japanese encephalitis virus infection, West Nile virus infection, and tick paralysis may resemble poliomyelitis. In Guillain-Barré syndrome (see Chapter 24), the weakness is more symmetric and ascending in most cases, but the Miller Fisher variant of Guillain-Barré is similar to bulbar poliomyelitis. Paresthesia is uncommon in poliomyelitis but common in Guillain-Barré syndrome. The CSF usually has high protein content but normal cell count in Guillain-Barré syndrome. While no evidence of poliomyelitis infection exists in acute flaccid myelitis that resembles polio, enteroviruses are isolated in some cases of acute flaccid myelitis.

► Treatment

In the acute phase of paralytic poliomyelitis, patients should be hospitalized. In cases of respiratory weakness or paralysis, intensive care is needed. Intensive physiotherapy may help recover some motor function with paralysis. Attention to psychological disorders in longstanding disease is also important.

Immunodeficient individuals have prolonged excretion of poliovirus leading to virus circulation and threatening the polio eradication efforts.

Immune modulators, such as prednisone, interferon, and IVIG, do not show any clear benefit in the treatment of post-poliomyelitis syndrome.

► Prognosis

The death-to-case ratio for paralytic polio ranges between 2% and 30%, depending on age. Bulbar poliomyelitis carries a mortality rate of up to 75%.

► Prevention

Given the epidemiologic distribution of poliomyelitis and the continued concern about vaccine-associated disease with the trivalent live OPV, the inactive (Salk) parenteral vaccine (IPV) is currently used in the United States for all four recommended doses (at ages 2 months, 4 months, 6–18 months, and at 4–6 years). Inactivated vaccine is also routinely used elsewhere in the developed world where one dose is often administered, although immunogenicity is improved with additional doses.

Because most of circulating vaccine-derived poliovirus and vaccine-associated poliomyelitis are live OPV type 2, the WHO replaced worldwide the trivalent live OPV (containing types 1, 2, and 3) with the bivalent live OPV

(type 1 and 3) in 2016. The goal is to replace all live OPV with inactive parenteral vaccination to eliminate poliovirus circulation. The advantages of oral vaccination are the ease of administration, low cost, effective local gastrointestinal and circulating immunity, and herd immunity. Monovalent OPV type 2 (mOPV2) as well as the trivalent OPV are used for control in countries with vaccine-derived type 2 outbreaks.

Routine immunization of adults in the United States is no longer recommended because of the low incidence of the disease. Vaccination should be considered for adults not vaccinated within the prior decade who are exposed to poliomyelitis or who plan to travel to endemic areas and adults engaged in high-risk activities (eg, laboratory workers handling stools).

► When to Refer

Any suspicious cases should be referred to public health authorities.

- Dyer O. Polio: WHO declares type 3 poliovirus eradicated after 31 year campaign. *BMJ*. 2019;367:l6201. [PMID: 31649018]
 Moffett DB et al. Progress toward poliovirus containment implementation—worldwide, 2019–2020. *MMWR Morb Mortal Wkly Rep*. 2020;69:1330. [PMID: 32941411]
 Pallansch MA. Ending use of oral poliovirus vaccine—a difficult move in the polio endgame. *N Engl J Med*. 2018;379:801. [PMID: 30157390]
 Razum O et al. Polio: from eradication to systematic, sustained control. *BMJ Glob Health*. 2019;4:e001633. [PMID: 31544903]

5. Acute Flaccid Myelitis



ESSENTIALS OF DIAGNOSIS

- ▶ Viral illness precedes neurologic signs.
- ▶ Flaccid paralysis usually affects upper limbs or all four limbs.
- ▶ Enterovirus is commonly isolated; poliomyelitis must be ruled out.

► General Considerations

Before widespread polio vaccination in the 1950s, polio was the most common cause of acute flaccid myelitis (also known as acute flaccid paralysis). More recently, nonpolio enteroviruses are most often the cause of acute flaccid myelitis. This disease has been reported throughout Africa (20 countries), the Eastern Mediterranean region (5 countries), intermittently in Europe (Germany and France), and the United States (48 states and the District of Columbia). The CDC began surveillance for acute flaccid myelitis in 2014. Since then, there have been three outbreaks in the United States. The largest to date occurred in 2018, with 80 confirmed cases between January 1, 2018, and November 1, 2018; all but 1 of the cases (99%) had a preceding viral illness in the month before presentation of neurologic signs. The neurologic signs most commonly

involved the upper limbs (47.5% of cases) or all four limbs (28.8% of cases). The most commonly associated viruses (among the 50 cases in which virus was isolated) were enterovirus A71 and enterovirus D68. In all instances, poliomyelitis was ruled out but an exact cause for the acute flaccid myelitis was not always determined.

► Clinical Findings

Acute flaccid myelitis is usually a childhood disease; the average age of presentation is 5 years. Cases usually present in late summer or early fall. There are three clinical stages of acute flaccid myelitis: a prodromal illness, followed by acute neurologic injury, and convalescence.

A. Symptoms and Signs

The prodrome typically consists of fever, upper respiratory symptoms, and gastrointestinal symptoms. One to four weeks later, neurologic symptoms begin and usually manifest as flaccid limb weakness with decreased reflexes. Fever may recur, and the patient experiences myalgia and flaccid weakness in one or more limbs. Upper extremities are affected more often than lower extremities. Once new neurologic symptoms have subsided, the convalescent phase can last for months to years. During this time, patients may experience residual muscle weakness and atrophy.

B. Laboratory Findings

Cerebrospinal fluid analysis shows pleocytosis (white blood cells greater than 5/mcL [$0.005 \times 10^9/L$]) often paired with elevated protein level (and a normal glucose concentration).

All individuals with suspected acute flaccid myelitis should be tested for enteroviruses (including D68 and A71) and rhinovirus from relevant anatomic sites. Testing for arboviruses, adenovirus, and herpesviruses should also be considered. All suspected cases should be reported to the state health department, the CDC, or both.

C. Imaging

MRIs of the brain and spinal cord should be accompanied by lumbar puncture. MRI typically shows disease of the central gray matter within the spinal cord in the location of the anterior horn cells.

► Treatment

No specific treatment exists for acute flaccid myelitis. Management consists of supportive care. Many adjunctive therapies have been used, including IVIG, high-dose corticosteroids, and plasmapheresis, but none have shown efficacy. Neurologists specializing in the management of acute flaccid myelitis can be contacted through the AFM Physician Consult and Support Portal at the following website: <https://bit.ly/2YU3VR>.

Several antiviral agents have been tested for efficacy against the viruses thought to cause this disease. Fluoxetine has in vitro activity against enterovirus D68; however, its use has not been associated with improved neurologic outcomes.

Long-term therapy during the convalescent phase should include physical therapy and any other necessary forms of physical rehabilitation.

► Prevention

An effective enterovirus-A71 vaccine has been developed for children and is in phase 3 trials (NCT03865238).

- Fatemi Y et al. Acute flaccid myelitis: a clinical overview for 2019. Mayo Clin Proc. 2019;94:875. [PMID: 31054607]
 Guan X et al. Effectiveness and safety of an inactivated enterovirus 71 vaccine in children aged 6–71 months in a phase IV study. Clin Infect Dis. 2020;71:2421. [PMID: 31734699]
 McKay SL et al. Increase in acute flaccid myelitis—United States, 2018. MMWR Morb Mortal Wkly Rep. 2018;67:1273. [PMID: 30439867]

OTHER NEUROTROPIC VIRUSES

1. Rabies



ESSENTIALS OF DIAGNOSIS

- ▶ History of animal bite.
- ▶ Paresthesias, hydrophobia, rage alternating with calm.
- ▶ Convulsions, paralysis, thick tenacious saliva.

► General Considerations

Rabies is a viral (rhabdovirus) encephalitis transmitted by infected saliva that enters the body by an animal bite or an open wound. Worldwide, over 17 million cases of animal bites are reported every year, and it is estimated that about 59,000 deaths annually are attributable to rabies. Rabies is endemic in over 150 countries; it is estimated that over 40% of the world's population lives in areas without rabies surveillance. Most cases of rabies occur in rural areas of Africa and Asia. India has the highest incidence, accounting for 36% of global deaths (<http://www.who.int/rabies/epidemiology/en/>). In developing countries, more than 90% of human cases and 99% of human deaths from rabies are secondary to bites from infected dogs. Rabies among travelers to rabies-endemic areas is usually associated with animal injuries (including dogs in North Africa and India, cats in the Middle East, and nonhuman primates in sub-Saharan Africa and Asia), with most travel-associated cases occurring within 10 days of arrival. Rabies-free areas include much of Western Europe, Australia, New Zealand, Japan, and the state of Hawaii in the United States. A map outlining these areas is available with Wikimedia Commons (https://commons.wikimedia.org/wiki/File:Rabies_Free_Countries_and_Territories.svg).

In the United States, domestically acquired rabies cases are rare (approximately 92% of cases are associated with wildlife) but probably underreported. Reports largely from the East Coast show an increase in rabies among cats, with

about 1% of tested cats showing rabies seropositivity. The annual caseload in the United States is 1–3 cases (https://www.cdc.gov/rabies/location/usa/surveillance/human_rabies.html). Between 1960 and 2018, a total of 125 human rabies cases were reported in the United States. These included 36 cases (28%) with a history of dog bites during international travel. The remaining 89 cases (72%) were acquired in the United States, most often by bats.

Surveillance for animal rabies in 2017 showed 4454 animal and 2 human cases occurring in 49 states and Puerto Rico. *Wild animals accounted for 91% of cases, and among wild animals, bats were the most common animal (31.2%).* Wildlife reservoirs, with each species having its own rabies variant(s), follow a unique geographic distribution in the United States: raccoons on the East Coast; skunks in the Midwest, Southwest, and California; and foxes in the Southwest and in Alaska. However, some areas have all three wildlife reservoirs (eg, the hill country of Texas). https://www.cdc.gov/rabies/location/usa/surveillance/wild_animals.html.

Raccoons, bats, and skunks accounted for 82% of the rabid animals found in the United States in 2017; other rabid animals include foxes, cats, cattle, and dogs. Rodents and lagomorphs (eg, rabbits) are unlikely to spread rabies because they cannot survive the disease long enough to transmit it (woodchucks and groundhogs are exceptions). Wildlife epizootics present a constant public health threat in addition to the danger of reintroducing rabies to domestic animals. Vaccination is the key to controlling rabies in small animals and preventing rabies transmission to human beings.

The virus enters the salivary glands of dogs 5–7 days before their death from rabies, thus limiting their period of infectivity. Less common routes of transmission include contamination of mucous membranes with saliva or brain tissue, aerosol transmission, and corneal transplantation. Recognized mutations in rabies virus proteins can subvert the host immune system. Transmission through solid organ and vascular segment transplantation from donors with unrecognized infection is also reported. A number of transplantation-associated cases are reported, including two clusters in the United States. Postexposure prophylaxis can be administered in these patients and may prevent development of disease.

The incubation period may range from 10 days to many years but is usually 3–7 weeks depending in part on the distance of the wound from the CNS. The virus travels via the nerves to the brain, multiplies there, and then migrates along the efferent nerves to the salivary glands. Rabies virus infection forms cytoplasmic inclusion bodies similar to Negri bodies. These Negri bodies are thought to be the sites of viral transcription and replication.

► Clinical Findings

A. Symptoms and Signs

While there is usually a history of animal bite, bat bites may not be recognized. The prodromal syndrome consists of pain at the site of the bite in association with fever, malaise, headache, nausea, and vomiting. The skin is sensitive to

changes of temperature, especially air currents (aerophobia). Percussion myoedema (a mounding of muscles after a light pressure stimulus) can be present and persist throughout the disease. Abnormal sexual behavior is also a recognized presenting symptom of rabies and such behavior includes priapism and frequent ejaculation in males and hypersexuality in females.

The CNS stage begins about 10 days after the prodrome and may be either encephalitic ("furious") or paralytic ("dumb"). The **encephalitic form** (about 80% of the cases) produces the classic rabies manifestations of delirium alternating with periods of calm, extremely painful laryngeal spasms on attempting drinking (hydrophobia), autonomic stimulation (hypersalivation), and seizures. In the less common **paralytic form**, an acute ascending paralysis resembling Guillain-Barré syndrome predominates with relative sparing of higher cortical functions initially. Both forms progress relentlessly to coma, autonomic nervous system dysfunction, and death.

B. Laboratory Findings

Biting animals that appear well should be quarantined and observed for 10 days. Sick or dead animals should be tested for rabies. A wild animal, if captured, should be sacrificed and the head shipped on ice to the nearest laboratory qualified to examine the brain for evidence of rabies virus. When the animal cannot be examined, raccoons, skunks, bats, and foxes should be presumed to be rabid.

Direct fluorescent antibody testing of skin biopsy material from the posterior neck of the potentially infected animal (where hair follicles are highly innervated) has a sensitivity of 60–80%.

Quantitative RT-PCR, nucleic acid sequence-based amplification, direct rapid immunohistochemical test, and viral isolation from the patient's CSF or saliva are advocated as definitive diagnostic assays. Antibodies can be detected in the serum and the CSF. Pathologic specimens often demonstrate round or oval eosinophilic inclusion bodies (Negri bodies) in the cytoplasm of neuronal cells, but the finding is neither sensitive nor specific. MRI signs are diffuse and nonspecific.

► Treatment & Prognosis

Management requires intensive care with attention to the airway, maintenance of oxygenation, and control of seizures. Universal precautions are essential. Corticosteroids are of no use. Survival is rare, and data are insufficient to provide estimate of success.

If postexposure prophylaxis (discussed below) is given expediently, before clinical signs develop, it is nearly 100% successful in prevention of disease. Once the symptoms have appeared, death almost inevitably occurs after 7 days, usually from respiratory failure. Most deaths occur in persons with unrecognized disease who do not seek medical care or in individuals who do not receive postexposure prophylaxis. The very rare cases in which patients recover without intensive care are referred to as "abortive rabies."

► Prevention

Immunization of household dogs and cats and active immunization of persons with significant animal exposure (eg, veterinarians) are important. The most important decisions, however, concern animal bites. Animals that are frequent sources of infection to travelers are dogs, cats, and nonhuman primates.

In the developing world, education, surveillance, and animal (particularly dog) vaccination programs (at recurrent intervals) are preferred over mass destruction of dogs, which is followed typically by invasion of susceptible feral animals into urban areas. In some Western European countries, campaigns of oral vaccination of wild animals led to the elimination of rabies in wildlife.

A. Local Treatment of Animal Bites and Scratches

Thorough cleansing, debridement, and repeated flushing of wounds with soap and water are important. Rabies immune globulin or antiserum should be given as stated below. Wounds caused by animal bites should not be sutured.

B. Postexposure Immunization

The decision to treat should be based on the circumstances of the bite, including the extent and location of the wound, the biting animal, the history of prior vaccination, and the local epidemiology of rabies. *Any contact or suspect contact with a bat, skunk, or raccoon is usually deemed a sufficient indication to warrant prophylaxis.* Consultation with state and local health departments is recommended. Postexposure treatment including both immune globulin and vaccination should be administered as promptly as possible when indicated.

For patients who had not received rabies vaccination prior to possible exposure, the optimal form of **passive immunization** is human rabies immune globulin (HRIG; 20 international units/kg), administered once. As much as possible of the full dose should be infiltrated around the wound, with any remaining injected intramuscularly at a site distant from the wound. Finger spaces can be safely injected without development of a compartment syndrome. If HRIG is not available and appropriate tests for horse serum sensitivity are done, equine rabies antiserum (40 international units/kg) can be used.

Two vaccines containing inactivated rabies viruses are licensed for **active immunization** and available for use in humans in the United States: a human diploid cell vaccine (Immavax) and a purified chick embryo cell vaccine (RabAvert). There are several postexposure prophylaxis strategies. The most commonly used one is the "abbreviated Essen" strategy, where either of the current vaccines is given as four intramuscular injections of 1 mL in the deltoid or, in small children, into the anterolateral thigh muscles on days 0, 3, 7, and 14 after exposure (the fifth dose at 28 days after exposure is no longer recommended except among immunosuppressed patients). The vaccine should not be given in the gluteal area due to suboptimal response. An alternative intramuscular vaccination strategy that takes only 1 week, with injections on days 0, 3, and

7 after exposure with a Vero cell vaccine (Verorab), was reportedly successful in achieving adequate neutralizing titers at days 14 and 28 in a study from Thailand; this vaccine is not currently available in the United States. Several new rabies vaccines are undergoing phase 1 clinical trials, including replication-defective chimpanzee adenovirus vaccines (ChAd155-RG and ChAdOx2 RabG) and a mRNA vaccine (CreVac CV7202).

The WHO supports an intradermal vaccination strategy using Verorab and the inactivated rabies virus vaccine Rabipur (an alternative formulation of the purified chick embryo cell) (0.1 mL per intradermal injection) for regions of the world where vaccine is in short supply; either vaccine can be given at two sites on days 0, 3, 7, and 28.

Rabies vaccines and HRIG should never be given in the same syringe or at the same site. Allergic reactions to the vaccine are rare and include a report of sudden unilateral sensorineural hearing loss and immune thrombocytopenic purpura, although local reactions (pruritus, erythema, tenderness) occur in about 25% and mild systemic reactions (headaches, myalgias, nausea) in about 20% of recipients. Rare cases of post-immunization encephalitis have been reported. Intradermal vaccines appear to be better tolerated than intramuscular vaccines, especially among young children (while titers achieved with intramuscular vaccinations are higher, the titers achieved with intradermal vaccination are deemed sufficient for protection against clinical rabies). The vaccines are commercially available or can be obtained through health departments. Adverse reactions to HRIG seem to be more frequent in women and rare in young children.

In patients with history of past vaccination, the need for HRIG is eliminated (HRIG is in short supply worldwide), but postexposure vaccination is still required. The vaccine should be given 1 mL in the deltoid twice (on days 0 and 3). Neither the passive nor the active form of postexposure prophylaxis is associated with fetal abnormalities and thus pregnancy is not considered a contraindication to vaccination. Peripartum rabies transmission occurs but is rare. Neonates may also receive both forms of postexposure prophylaxis at birth.

The WHO has a program to eliminate dog-transmitted human rabies by 2030.

C. Preexposure Immunization

Preexposure prophylaxis with three injections of human diploid cell (Immovax) vaccine intramuscularly (1 mL on days 0, 7, and 21 or 28) is recommended for persons at high risk for exposure: veterinarians (who should have rabies antibody titers checked every 2 years and be boosted with 1 mL intramuscularly); animal handlers; laboratory workers; Peace Corps workers; and travelers with stays over 1 month to remote areas in endemic countries in Africa, Asia, and Latin America. An intradermal route is also available (0.1 mL on days 0, 7, and 21 over the deltoid) but not in the United States. Intradermal administration of a double dose of 0.1 mL on days 0 and 7 is safe and as effective as the three-dose schedule. Immunosuppressive illnesses and agents including corticosteroids as well as antimalarials—in particular chloroquine—may diminish

the antibody response. A single-dose booster at 10 years after initial immunization increases the level of antibody titers. Unfortunately, data from travel services indicate that only a small proportion of travelers with anticipated lengthy stays in rabies-impacted areas receive the vaccine as recommended.

► When to Refer

Suspicion of rabies requires contact with public health personnel to initiate appropriate passive and active prophylaxis and observation of suspect cases.

► When to Admit

- Respiratory, neuromuscular, or CNS dysfunction consistent with rabies.
- Patients with suspect rabies require initiation of therapy until the disease is ruled out in suspect animals, and this requires coordination of care based on likelihood of patient compliance, availability of inpatient and outpatient facilities, and response of local public health teams.

Pieracci EG et al. Vital Signs: Trends in human rabies deaths and exposures—United States, 1938–2018. MMWR Morb Mortal Wkly Rep. 2019;68:524. [PMID: 31194721]

Soentjens P et al. Preexposure intradermal rabies vaccination: a noninferiority trial in healthy adults on shortening the vaccination schedule from 28 to 7 Days. Clin Infect Dis. 2019;68:607. [PMID: 29939243]

Tian Z et al. Clinical features of rabies patients with abnormal sexual behaviors as the presenting manifestations: a case report and literature review. BMC Infect Dis. 2019;19:679. [PMID: 31370800]

2. Arbovirus Encephalitides

ESSENTIALS OF DIAGNOSIS

- ▶ Acute febrile illness; rash may be present; stiff neck progressing to stupor, coma, and convulsions.
- ▶ Upper motor neuron lesion signs: exaggerated deep tendon reflexes, absent superficial reflexes, and spastic paraparesis.
- ▶ CSF opening pressure and protein are often increased with lymphocytic pleocytosis.

► General Considerations

The arboviruses are arthropod-borne viral pathogens carried by mosquitoes or ticks that produce clinical manifestations in humans. The **mosquito-borne pathogens** include togaviruses (most of which are of the genus *Alphavirus*, including Western, Eastern, Venezuelan equine encephalitis, chikungunya, and Mayaro virus), flaviviruses (West Nile, St. Louis encephalitis, Japanese encephalitis, Murray Valley encephalitis, dengue, Zika, yellow fever, and Rocio viruses), orthobunyaviruses (the California serogroup

viruses, including the Jamestown Canyon [seen largely in Northeastern states], La Crosse [seen in the upper Midwest and mid-Atlantic primarily], and Keystone viruses). The **tick-borne** causes of encephalitis include the flaviviruses Powassan virus (North American Northeast and Great Lakes) and tick-borne encephalitis virus (Europe and Asia), as well as the Colorado tick fever reovirus. Only those viruses causing primarily encephalitis in the United States are discussed here. The most commonly encountered arboviruses from 2018 in the United States are West Nile virus (2647 cases, 92% of arboviral neuroinvasive disease), Jamestown Canyon virus (41 cases), the La Crosse virus (86 cases), and Powassan virus (21 cases). Rare causes of domestic arboviruses were St. Louis encephalitis virus (8 cases) and eastern equine encephalitis virus disease (6 cases).

West Nile virus is the leading cause of domestically acquired arboviral disease in the United States. West Nile virus disease is a nationally notifiable condition. Among the 958 cases reported in 2019, based on preliminary data from the CDC from 48 states and the District of Columbia, 626 (65%) were classified as neuroinvasive disease. The states reporting the most cases of neuroinvasive disease are in the west and southwest and include California (147 cases), Arizona (136 cases), Colorado (52 cases), Nevada (33 cases), and New Mexico (30 cases). Asymptomatic seroconversion is the norm and is not reported.

Outbreaks with West Nile infection tend to occur between mid-July and early September. Climatic factors, including elevated mean temperatures and rainfall, correlate with increased West Nile infection. West Nile virus circulates between mosquitoes (mainly *Culex* species) and birds. In case of West Nile virus outbreak, infected birds develop high level viremia that leads to substantial avian mortality and a high incidence of mosquito infection. Infected mosquitoes bite and infect people and other mammals. However, humans and other mammals are “dead end” hosts since they do not transmit the virus on to other biting mosquitoes; only dengue and Venezuelan equine encephalitis viruses produce viremias high enough to allow continued transmission to other mosquitoes and ticks between humans and vectors. Human-to-human transmission is usually related to blood transfusion and organ transplantation. Since 2003, all blood donations in the United States are screened with nucleic acid amplification assays for West Nile virus. Eastern equine encephalitis is now also shown to be transmitted by organ transplantation.

► Clinical Findings

A. Symptoms and Signs

West Nile virus infection has an incubation period of 2–14 days. The infection is symptomatic in about 20% of the cases and less than 1% progress to neuroinvasive disease, including meningitis, encephalitis, and flaccid paralysis. The case fatality rate is 3–15% in symptomatic patients.

Symptoms include acute febrile illness, and a nonpruritic maculopapular rash is variably present. Meningitis is indistinguishable from other viral meningitis. West Nile

virus encephalitis presents with fever and altered mental status. Other signs include tremors, seizures, cranial nerve palsies, and pathologic reflexes. Acute flaccid (poliomyelitis-like) paralysis, which is asymmetric and can involve facial and respiratory muscles, is a well-known complication and is less commonly seen with other arboviruses infection. West Nile virus can also present as Guillain-Barré syndrome with radiculopathy. The disease manifestations associated with West Nile virus infection are strongly age-dependent: the acute febrile syndrome and mild neurologic symptoms are more common in the young, aseptic meningitis and poliomyelitis-like syndromes are seen in middle-aged persons, and frank encephalopathy is seen more often in older adults. All forms of disease tend to be severe in immunocompromised persons in whom neuroinvasive manifestations and associated high mortality are more apt to develop. Other risk factors for development of neuroinvasive disease and increased mortality include Black race, diabetes, chronic kidney disease, and hepatitis C virus infection.

Host genetic variation in the interferon response pathway is associated with both risk for symptomatic West Nile virus infection and increased likelihood of West Nile virus disease progression.

B. Laboratory Findings

The peripheral white blood cell count is typically normal. Usually a CSF lymphocytic pleocytosis is present, and polymorphonuclear cells predominate early. The diagnosis of arboviral encephalitides depends on serologic tests. For West Nile virus, an IgM capture ELISA in serum or CSF is almost always positive by the time the disease is clinically evident, and the presence of IgM in CSF indicates neuroinvasive disease. Documentation of a fourfold increase in acute/convalescent IgG titers is confirmatory for all arboviruses. Antibodies to arboviruses persist for life, and the presence of IgG in the absence of a rising titer of IgM may indicate past exposure rather than acute infection. Serologic tests are available commercially and through local and state health departments. Cross-reactivity exists among the different flaviviruses, so a plaque reduction assay may be needed to definitively distinguish between West Nile fever, St. Louis encephalitis, and others. PCR assays (available through state laboratories and the CDC) can be used to detect viral RNA in serum, CSF, or tissue early after illness onset and may be particularly useful in immunocompromised patients with abnormal antibody responses. Blood products are best screened using nucleic acid assays. MRI of the brain may reveal leptomeningeal, basal ganglia, thalamic, or periventricular enhancement.

► Differential Diagnosis

Mild forms of encephalitis must be differentiated from aseptic meningitis, lymphocytic choriomeningitis, and nonparalytic poliomyelitis.

Severe forms of arbovirus encephalitides are to be differentiated from other causes of viral encephalitis (HSV, mumps virus, poliovirus or other enteroviruses, HIV),

encephalitis accompanying exanthematous diseases of childhood (measles, varicella, infectious mononucleosis, rubella), encephalitis following vaccination or infection (a demyelinating type seen after rabies, measles, pertussis vaccination), toxic encephalitis (from drugs, poisons, or bacterial toxins such as *Shigella dysenteriae* type 1), Reye syndrome, and severe forms of stroke, brain tumors, brain abscess, autoimmune processes such as lupus cerebritis, and intoxications. In the California Encephalitis Project, anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a more common cause of encephalitis than viral diseases, especially in the young, with 65% of cases of encephalitis due to anti-NMDAR occurring among patients 18 or younger.

► Complications

Bronchial pneumonia, urinary retention and infection, prolonged weakness, and pressure injuries may occur. Retinopathy occurs in 24% of patients with a history of West Nile virus infection and is associated with increased risk in those with encephalitis. Individuals with chronic symptoms after West Nile virus infection may show persistent kidney infection for up to 6 years with West Nile virus RNA present in urine; kidney infection may lead to progressive renal pathology.

► Treatment

Although specific antiviral therapy is not available for most causative entities, vigorous supportive measures can be helpful. Some studies suggest improved outcomes with the use of IVIG enriched with West Nile virus antibody; however, a randomized, controlled trial of IVIG did not show a benefit.

► Prognosis

Although most infections are mild or asymptomatic, the prognosis is always guarded, especially at the extremes of age. Most fatalities occur with neuroinvasive disease. The majority of patients with non-neuroinvasive West Nile virus disease or West Nile virus meningitis recover completely, but a syndrome of fatigue, malaise, and weakness can linger for weeks or months. Patients who recover from West Nile virus encephalitis or poliomyelitis often have residual neurologic deficits. The recovery of persons with severe neurologic compromise may take 6 months or longer. The sequelae of West Nile virus infection include a poliomyelitis-like syndrome, cognitive complaints, movement disorders, epilepsy, and depression; and they may become apparent late in the course of what appears to be a successful recovery.

Another entity (nonprimary infection), characterized by elevated serum IgG, absent serum IgM, and occasional detection of West Nile virus RNA in blood or CSF, is associated with underlying psychiatric disorders, hospitalization during times not associated with peak West Nile transmission, fever, and increased in-hospital mortality.

The long-term prognosis is generally better for Western equine than for Eastern equine or St. Louis encephalitis.

► Prevention

Mosquito avoidance (repellents, protective clothing, and insecticide spraying) is effective prevention. Laboratory precautions are indicated for handling all these pathogens. No human vaccine is currently available for the arboviruses prevalent in North America. A chimeric live attenuated West Nile virus vaccine is tested in phase 2 clinical trials and is shown to be safe and immunogenic in healthy adults.

Lednicky JA et al. Keystone virus isolated from a Florida teenager with rash and subjective fever: another endemic arbovirus in the southeastern United States? *Clin Infect Dis*. 2019;68:143. [PMID: 29893806]

McDonald E et al. West Nile virus and other domestic nationally notifiable arboviral diseases—United States, 2018. *MMWR Morb Mortal Wkly Rep*. 2019;68:673. [PMID: 31393865]

Morens DM. Eastern equine encephalitis virus—another emergent arbovirus in the United States. *N Engl J Med*. 2019;381:189. [PMID: 31747726]

Musso D et al. Unexpected outbreaks of arbovirus infections: lessons learned from the Pacific and tropical America. *Lancet Infect Dis*. 2018;18:e355. [PMID: 29934112]

3. Japanese Encephalitis

ESSENTIALS OF DIAGNOSIS

- Most important vaccine-preventable cause of encephalitis in the Asia-Pacific region.
- The virus is transmitted by mosquitoes, especially *Culex* species.
- Wide symptom spectrum; most infections asymptomatic.

► General Considerations

The Japanese encephalitis virus is a flavivirus akin to those causing West Nile infection and St. Louis encephalitis. It is the most common cause of encephalitis in East Asia with over 68,000 estimated annual cases and up to 20,400 annual deaths. It is geographically confined to East Asia and the Western Pacific. Most cases occur in the summer and late fall, although in tropical and subtropical areas transmission occurs throughout the year. Major outbreaks every 2–15 years often correlate with patterns of agricultural development. The virus is transmitted by mosquitoes, especially *Culex* species. Areas with high endemicity tend to be warm-temperate, semitropical or tropical areas with high annual rainfalls. Wading birds (such as herons) and pigs more commonly sustain the infection as reservoirs in nature, since the viremia in humans is transient and not usually high enough to sustain transmission. In endemic countries, Japanese encephalitis is primarily a disease of children. Travelers to major urban areas for less than 1 month are at minimal risk for Japanese encephalitis. Transmission by blood transfusion is documented.

► Clinical Findings

A. Symptoms and Signs

The median incubation period is 5–15 days. Most persons asymptotically seroconvert. The 1% of patients in whom disease develops report sudden-onset headaches, nausea, and vomiting, followed by mental status changes, parkinsonian movement disorders, and in a smaller percentage, seizures, typically in children.

Japanese encephalitis most closely resembles St. Louis encephalitis and West Nile encephalitis, although epidemiologic data readily distinguish these infections in most instances. The clinical course is less severe in patients with a history of dengue virus infection.

B. Laboratory Findings and Diagnosis

The disease should be suspected in persons with symptoms of CNS infection who recently visited or who reside in an endemic area.

Common laboratory abnormalities include leukocytosis, mild anemia, and hyponatremia. CSF typically has a mild to moderate pleocytosis with a lymphocytic predominance, slightly elevated protein, and normal glucose.

Diagnosis is confirmed by finding anti-Japanese encephalitis virus IgM in CSF or serum using ELISA. Definitive diagnosis requires fourfold increase in virus-specific IgG confirmed by plaque reduction neutralization assay. Because of low levels of viremia in humans, RT-PCR is not recommended.

In severe disease, brain imaging reveals thalamic lesions, with the hippocampus, midbrain, basal ganglia, and cerebral cortex affected to varying degrees.

► Complications

A variety of cognitive, neurologic, and psychiatric complications, including memory impairment and intellectual impairment in adults and children, are recognized to occur in as many as 50% of survivors and to persist at least 1–2 years after the acute infection. Opsoclonus myoclonus syndrome is rarely reported. The mortality is as high as 30%.

► Treatment

Treatment is supportive, including antipyretics, analgesics, bed rest, and fluids. Corticosteroids may result in clinical improvement of opsoclonus myoclonus syndrome.

► Prevention

Using mosquito repellents; wearing long sleeves, long pants, and socks; and using air-conditioned facilities and bed nets are essential means of protection.

In the United States, inactivated Vero-cell culture-derived Japanese encephalitis vaccine (IXIARO) is licensed for the prevention of Japanese encephalitis in persons 2 months of age and older. Travelers who plan to spend more than 1 month in endemic areas should receive the vaccine. Vaccine should also be considered for travelers who plan to spend less than 1 month in endemic areas but

who are at increased risk for Japanese encephalitis (eg, season, location, activities). Primary vaccination requires two doses administered 28 days apart, to be completed more than 1 week before travel. For adults, a booster dose is recommended in case of potential reexposure or of continued risk for infection if the primary series of the vaccine was administered over a 1 year before.

Four effective types of vaccine against Japanese encephalitis are available worldwide, including live attenuated and inactivated vaccines. The risk of serious reactions, including potential encephalitis with live vaccines, is low and decreases with age. Rare reported neurologic reactions are not definitively associated with vaccination. There are no studies about the safety of IXIARO in pregnant women. Therefore, administration of this vaccine to pregnant women should be deferred, unless the risk of infection outweighs the risk of vaccine complications.

Barzon L et al. Recent developments in vaccines and biological therapies against Japanese encephalitis virus. *Expert Opin Biol Ther.* 2018;18:851. [PMID: 29991325]

Caldwell JP et al. Evolving epidemiology of Japanese encephalitis: implications for vaccination. *Curr Infect Dis Rep* 2018; 20:30. [PMID: 2959548]

Cheng VCC et al. Japanese encephalitis virus transmitted via blood transfusion, Hong Kong, China. *Emerg Infect Dis.* 2018;24:49. [PMID: 29043965]

Hills SL et al. Japanese encephalitis vaccine: recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep.* 2019;68:1. [PMID: 31518342]

World Health Organization. Japanese encephalitis: fact sheet. May 2019. <https://www.who.int/news-room/fact-sheets/detail/japanese-encephalitis>

4. Tick-Borne Encephalitis

ESSENTIALS OF DIAGNOSIS

- Flaviviral encephalitis found in Eastern, Central, and occasionally Northern Europe and Asia.
- Transmitted via ticks or ingestion of unpasteurized milk.
- Long-term neurologic sequelae in 2–25% of cases.
- Therapy is largely supportive.
- Prevention: avoid tick exposure, pasteurize milk, and vaccinate.

► General Considerations

Tick-borne encephalitis (TBE) is a flaviviral infection caused by TBE virus with three subtypes: **European**, **Siberian**, and **Far Eastern**. The principal reservoirs and vectors for TBE virus are ticks with small rodents as the amplifying host; humans are an accidental host. The vectors for most cases are *Ixodes ricinus* (European subtype) and *Ixodes persulcatus* (Siberian and Far Eastern subtype). Infection results from tick bites during outdoor activities in forested areas, predominantly in the late spring through

fall. Ingestion of unpasteurized milk from viremic livestock (goats, sheep, and cattle) is also a recognized mode of transmission. Transmission by transplantation of solid organs is reported leading to fatal outcomes. TBE is endemic in certain parts of Europe (where its prevalence has been expanding in recent years; eg, in 2018, 377 cases were recorded in Switzerland, 40% more than in 2017) and Asia (principally China but a few cases from Japan as well). The number of cases reported annually fluctuates significantly depending on surveillance, human activities, socio-economic factors, ecology, and climate. The incubation period is 7–14 days for tick-borne exposures but only 3–4 days for milk ingestion.

Powassan virus is the only North American member of the tick-borne encephalitides. Its vector is several *Ixodes* species ticks. Most cases occur in older men (median age, 62; all deaths have occurred in persons over age 50), primarily from Northeast and North Central states (especially Minnesota, New York, and Wisconsin). Most reported cases are neuroinvasive with presentations including acute encephalitis and aseptic meningitis. The incubation period can range from 1 to 5 weeks, although pinpointing the date of actual exposure is often difficult.

Alkhurma hemorrhagic fever is also caused by a flavivirus first uncovered in Jeddah, Saudi Arabia, in 1995 and is reemerging in the Middle East with occurrences in tourists to Egypt, Djibouti, and possibly India. Its extent of geographic distribution is currently unknown.

B. Laboratory Findings and Diagnosis

Leukopenia alternating with leukocytosis can be seen. Abnormal CSF findings include an inconsistent pleocytosis that may persist for up to 4 months. Hyponatremia is more commonly seen than with other viral encephalitides. Neuroimaging might show hyperintense lesions in the thalamus, brainstem, and basal ganglia, and cerebral atrophy.

When neurologic symptoms develop, the TBE virus is typically no longer detectable in blood and CSF samples. Virus detection by RT-PCR in ticks from TBE patients, if available, can help with the diagnosis. TBE virus IgM and IgG are detected by ELISA when neurologic symptoms occur.

Cross-reactivity with other flaviviruses or a vaccinated state may require confirmation by detection of TBE virus-specific antibodies by plaque-reduction neutralization tests.

► Differential Diagnosis

The differential diagnosis includes other causes of aseptic meningitis, such as enteroviral infections; poliomyelitis (no longer reported from Eastern Europe); herpes simplex encephalitis; and a variety of tick-borne pathogens, including tularemia, the rickettsial diseases, babesiosis, Lyme disease, and other flaviviral infections. Coinfections are documented with *Anaplasma*, *Babesia*, and *Borrelia* infections.

► Treatment

No specific antiviral treatment is available, and therapy is largely supportive.

► Prognosis

The three subtypes of TPE have different prognoses. The European subtype is usually milder with up to 2% mortality and 30% neuroinvasive disease. The Siberian subtype is associated with 3% mortality and chronic, progressive disease. The Far Eastern subtype is usually more severe with up to 40% mortality and higher likelihood of neurologic involvement. All three subtypes are more severe among elderly adults compared with children. Coinfection with *Borrelia burgdorferi* (the agent of Lyme disease; transmitted by the same tick vector) may result in more severe disease.

► Prevention

No TBE vaccine is available in the United States. There are four inactivated TBE virus vaccines for adults and children licensed in Europe (two in Austria and Germany and two in Russia) and one available in China. The vaccine is safe and effective and should provide cross-protection against all three TBE virus subtypes. The initial vaccination schedule requires two to three doses given over 6 or more months with boosters every 1–5 years, the interval dependent on the vaccine and national guidelines. Breakthrough TBE in vaccinated individuals is reported, especially among recipients who are over 50 years of age and among

► Clinical Findings

A. Symptoms and Signs

Most cases are subclinical, and many resemble an influenza-like syndrome with 2–10 days of fever (usually with malaise, headache, and myalgias). In some cases, the disease is biphasic where the initial flu-like period is followed by a 1- to 21-day symptom-free interval followed by a second phase with fevers and neurologic symptoms (cases from Asia appear not to show this biphasic pattern). The neurologic manifestations range from febrile headache to aseptic meningitis and encephalitis with or without myelitis (preferentially of the cervical anterior horn) and spinal paralysis (usually flaccid). A myeloradiculitic form can also develop but is less common. Peripheral facial palsies, sometimes bilateral, tend to occur infrequently late in the course of infection, usually after encephalitis and generally are associated with a favorable outcome within 30–90 days. The main sequela of disease is paresis. Other causes of long-term morbidity include protracted cognitive dysfunction and persistent spinal nerve paralysis. The **post-encephalitic syndrome** is characterized by headache, difficulties concentrating, balance disorders, dysphasia, hearing defects, and chronic fatigue. A progressive motor neuron disease and partial continuous epilepsy are complications. Longstanding psychiatric complications are reported and include attention deficits, slowness of thought and learning impairment, depression, lability, and mutism.

Mortality in TBE is usually a consequence of brain edema or bulbar involvement.

persons who are immunosuppressed, such as those receiving anti-TNF therapy or methotrexate, indicating the need for a modified immunization strategy in such patients. Data support adding an extra booster vaccine dose for individuals aged 50 years and older. Neuritis and neuropathies of peripheral nerves (plexus neuropathy—paresis of lower limb muscles, polyradiculopathy) are recognized complications of TBE vaccination.

The low popular support for the vaccine in endemic countries is responsible for limited abilities to control the disease. Other prevention recommendations include avoidance of tick exposure and pasteurization of cow and goat milk.

Fischer M et al. Tickborne encephalitis. In: Centers for Disease Control and Prevention. Chapter 3 (83): CDC Health Information for International Travel 2018. New York: Oxford University Press, 2018. <https://wwwnc.cdc.gov/travel/yellowbook/2018/infectious-diseases-related-to-travel/tickborne-encephalitis>

Hansson KE et al. Tick-borne encephalitis (TBE) vaccine failures: a ten-year retrospective study supporting the rationale for adding an extra priming dose in individuals at age 50 years. *Clin Infect Dis*. 2020;70:245. [PMID: 30843030]

Krow-Lucal ER et al. Powassan virus disease in the United States, 2006–2016. *Vector Borne Zoonotic Dis*. 2018;18:286. [PMID: 29652642]

Kunze U et al. Report of the 21st Annual Meeting of the International Scientific Working Group on Tick-Borne Encephalitis (ISW-TBE): TBE - record year 2018. *Ticks Tick Borne Dis*. 2020;11:101287. [PMID: 31522919]

Tambo E et al. Defeating re-emerging Alkhurma hemorrhagic fever virus outbreak in Saudi Arabia and worldwide. *PLoS Negl Trop Dis*. 2018;12:e0006707. [PMID: 30260960]

5. Lymphocytic Choriomeningitis

ESSENTIALS OF DIAGNOSIS

- ▶ “Influenza-like” prodrome of fever, chills, and cough, followed by a meningeal phase.
- ▶ Aseptic meningitis: stiff neck, headache, vomiting, lethargy.
- ▶ CSF: slight increase of protein, lymphocytic pleocytosis ($500\text{--}3000/\text{mCL}$ [$0.5\text{--}3.0 \times 10^9/\text{L}$]).
- ▶ Complement-fixing antibodies within 2 weeks.

General Considerations

The lymphocytic choriomeningitis virus is an arenavirus (related to the pathogen causing Lassa fever, discussed below) that primarily infects the CNS. Its main reservoir is the house mouse (*Mus musculus*). Other rodents (such as rats, guinea pigs, and even pet hamsters), monkeys, dogs, and swine are also potential reservoirs. The infected animal sheds lymphocytic choriomeningitis virus in nasal secretions, urine, and feces; transmission to humans probably occurs through aerosolized particles and mucosal exposure, percutaneous inoculation, direct contact, or animal

bites. The disease in humans is underdiagnosed and occurs most often in autumn. The lymphocytic choriomeningitis virus is typically not spread person to person, although vertical transmission is reported, and it is considered to be an underrecognized teratogen. Rare cases related to solid organ transplantation and autopsies of infected individuals are also reported. All reported cases were donor derived. Outbreaks are uncommon, and usually occur in laboratory settings among those workers with significant rodent exposure.

The ubiquitous nature of its reservoir and the large distribution of the reported cases suggest a widespread geographic risk of lymphocytic choriomeningitis virus infection. Serologic surveys in the southern and eastern United States suggest past infection in approximately 3–5% of those tested, although later data from upstate New York showed less than 1% seroprevalence. Infection risk can be reduced by limiting contact with pet rodents and rodent trappings.

Clinical Findings

A. Symptoms and Signs

The incubation period is 8–13 days to the appearance of systemic manifestations and 15–21 days to the appearance of meningeal symptoms. Symptoms are biphasic, with a prodromal illness characterized by fever, chills, headache, myalgia, cough, and vomiting, occasionally with lymphadenopathy and maculopapular rash. After 3–5 days, the fever subsides only to return after 2–4 days along with the meningeal phase, characterized by headache, nausea and vomiting, lethargy, and variably present meningeal signs. Arthralgias can develop late in the course. Transverse myelitis, deafness, Guillain-Barré syndrome, and transient and permanent hydrocephalus are reported. Lymphocytic choriomeningitis virus is a well-known, albeit underrecognized, cause of congenital infection frequently complicated with obstructive hydrocephalus and chorioretinitis. In fetuses and newborns with ventriculomegaly or other abnormal neuroimaging findings, screening for congenital lymphocytic choriomeningitis may be considered; mothers are asymptomatic half the time. In over one-third of cases, rodent exposure is reported retrospectively. Occasionally, a syndrome resembling the viral hemorrhagic fevers is described in transplant recipients of infected organs and in patients with lymphoma.

B. Laboratory Findings

Leukocytosis or leukopenia and thrombocytopenia may be initially present. During the meningeal phase, CSF analysis frequently shows lymphocytic pleocytosis (total count is often $500\text{--}3000/\text{mCL}$ [$0.5\text{--}3.0 \times 10^9/\text{L}$]) with a slight increase in protein, while a low to normal glucose is seen in at least 25%. The virus may be recovered from the blood and CSF by mouse inoculation. Complement-fixing antibodies appear during or after the second week. Detection of specific IgM by ELISA is widely used. Detection of lymphocytic choriomeningitis virus by PCR is available in research settings.

► Differential Diagnosis

The influenza-like prodrome and latent period may distinguish this from other aseptic meningitides, and bacterial and granulomatous meningitis. A history of exposure to mice or other potential vectors is an important diagnostic clue.

► Treatment

Treatment is supportive. In several survivors of transplant-associated outbreaks, ribavirin (which is effective against other arenaviruses) has been used successfully along with decreasing immunosuppression.

► Prognosis

Complications and fatalities are rare in the general population. The illness usually lasts 1–2 weeks, though convalescence may be prolonged. Lymphocytic choriomeningitis in solid organ transplant recipients is associated with a poor prognosis; the mortality rate may exceed 80%.

► Prevention

Pregnant women should be advised of the dangers to their unborn children inherent in exposure to rodents.

Tanveer F et al. Lymphocytic choriomeningitis virus meningo-encephalitis in a renal transplant recipient following exposure to mice. *Transpl Infect Dis.* 2018;29:e13013. [PMID: 30325104]

6. Prion Diseases

ESSENTIALS OF DIAGNOSIS

- Rare in humans.
- Cognitive decline.
- Myoclonic fasciculations, ataxia, visual disturbances, pyramidal and extrapyramidal symptoms.
- Variant form presents in younger persons with prominent psychiatric or sensory symptoms.
- Specific EEG patterns.

► General Considerations

The transmissible spongiform encephalopathies are a group of fatal neurodegenerative diseases affecting humans and animals. They are caused by proteinaceous infectious particles or prions. These agents show slow replicative capacity and long latent intervals in the host. They induce the conformational change (“misfolding”) of a normal brain protein (prion protein; PrP[C]) into an abnormal isoform (PrP[Sc]) that accumulates and causes neuronal vacuolation (spongiosis), reactive proliferation of astrocytes and microglia, and, in some cases, the deposition of beta-amyloid oligomeric plaques.

Prion disease can be hereditary, sporadic, or transmissible in humans. Hereditary disorders are caused by germ line mutations in the PrP[C] gene causing familial Creutzfeldt-Jakob disease (fCJD), Gerstmann-Sträussler-Scheinker syndrome (GSS), and fatal familial insomnia. Another uncommon hereditary disorder is PrP systemic amyloidosis.

Sporadic Creutzfeldt-Jakob disease (sCJD) is the most common of the human prion diseases, accounting for approximately 85% of cases; it has no known cause. Transmissible prion disease is described only for kuru and Creutzfeldt-Jakob disease in its **iatrogenic (iCJD)** and **variant (vCJD)** form. Iatrogenic transmission of CJD is associated with prion contaminated human corneas, dura mater grafts, pituitary-derived growth hormone, gonadotropins, stereotactic electroencephalography, electrodes, and neurosurgical instruments. Abnormal prion proteins have been detected in the nasal mucosa and urine of patients with Creutzfeldt-Jakob disease, raising health concerns about possibility of transmission.

Kuru, once prevalent in central New Guinea, is now rare, a decline in prevalence that started after the abandonment of cannibalism in the late 1950s (a protective allele of the PrP gene is now identified at codon 127).

More than 200 cases of vCJD (**bovine spongiform encephalopathy** [BSE] or “mad cow disease”) were reported in the United Kingdom since the first documented cases there in the mid-1990s. It is far less common in North America, with only four cases reported in the United States (the last one in 2015) and two deaths in Canada from definite or probable vCJD. Of the US-reported cases, none are confirmed to have acquired the disease locally (two of them acquired the infection in the United Kingdom, one in Saudi Arabia, one possibly in a Middle Eastern or Eastern European country). The overall annual incidence of prion disease worldwide is approximately 1–2 persons per million. This disease is characterized by its bovine-to-human transmission through ingestion of meat from cattle infected with BSE. There is no animal-to-animal spread of BSE, and milk and its derived products are not considered infectious. Reports of secondary transmission of vCJD due to blood transfusions from asymptomatic donors are reported in the United Kingdom. Although iCJD and vCJD are not associated with a known PrP gene mutation, a polymorphism in codon 129 is prevalent and seems to determine susceptibility and expression of clinical disease.

A **chronic wasting disease** also due to a transmissible spongiform encephalopathic agent is increasing; occurs among deer, elk, and moose; and is reported from 26 states including most of Wyoming and parts of Colorado but present in the East and South as well. Although there are no documented cases of transmission to humans, transmission in the laboratory to squirrel monkeys has occurred, and the CDC recommends refraining from killing bizarrely acting animals, not handling or eating roadkill, and wearing gloves when dressing wild game. Testing for the virus in game animals may be useful, but its efficacy is not established.

► Clinical Findings

A. Symptoms and Signs

Both sCJD and fCJD usually present in the sixth or seventh decade of life, whereas the iCJD form tends to occur in a much younger population. Clinical features of these three forms of disease usually involve mental deterioration (dementia, behavioral changes, loss of cortical function) that is progressive over several months, as well as myoclonus and extrapyramidal (hypokinesia) and cerebellar manifestations (ataxia, dysarthria). Finally, coma ensues, usually associated with an akinetic state and less commonly decerebrate/decorticate posturing. Like iCJD, vCJD usually affects younger patients (averaging ~28 years), but the duration of disease is longer (about 1 year). The degree of organ involvement is often extensive, and the clinical symptoms are unique, mainly characterized by prominent psychiatric and sensory symptoms.

B. Laboratory Findings

CJD should be diagnosed in the proper clinical scenario, in the absence of alternative diagnoses after routine investigations. Abnormalities in CSF are subtle and rarely helpful. The detection of 14-3-3 protein in the CSF is helpful for the diagnosis of sCJD but not in vCJD and fCJD. Its sensitivity and specificity are widely variable among different studies and may be increased with use of tau protein assays. CSF detection of total PrP can differentiate CJD from atypical Alzheimer disease with 82% sensitivity and 91% specificity.

A blood-based assay and PCR in CSF may help with the diagnosis of vCJD with high specificity but 71% sensitivity. The assay as well as 14-3-3 protein assay and a “quaking induced conversion” assay are all available through the National Prion Disease Surveillance Center at Case Western University in Cleveland. Other referral laboratories with variable availability of assays include state health departments, academic centers, and the National Prion Clinics in the United Kingdom. It is also recognized that the presence of a variant with low titers (“very low peripheral prion colonization”) in peripheral tissue, including frequently biopsied tonsillar tissue, may be responsible for the underrecognition of vCJD.

Probable diagnosis requires the presence of rapidly progressive dementia plus two of four clinical features (myoclonus, visual or cerebellar signs, pyramidal/extrapyramidal signs, and akinetic mutism) as well as a positive laboratory assay (typical EEG, positive 14-3-3 CSF assay with duration under 2 years) and MRI high signal in the caudate and/or putamen on diffusion-weighted imaging (DWI) or fluid-attenuated inversion recovery (FLAIR) imaging. In sCJD, the EEG typically shows a pattern of paroxysms with high voltages and slow waves, while the MRI is characteristic for bilateral areas of increased signal intensity, predominantly in the caudate and putamen. An MRI can improve early diagnosis of sCJD because clinical findings are often missed. When an experienced neuroradiologist or a prion disease expert reviews the MRI, diagnostic sensitivity of MRI for sCJD increases to 91%.

► Differential Diagnosis

Autoimmune encephalitis can have a similar clinical picture. The presence of high titer autoantibodies (eg, to the NMDA receptor) in the CSF is consistent with autoimmune encephalitis.

► Treatment & Prevention

There is no specific treatment for CJD. Once symptoms appear, the infection invariably leads to death. Flupirtine (an analgesic medication) is sometimes useful in slowing the associated cognitive decline but does not affect survival. Quinacrine (mepacrine) was not shown to improve survival for people with sCJD. Antibodies against PrP are also proposed as a therapeutic strategy. Studies are in progress to identify epitopes for vaccine development, but no promising candidates exist to date.

Iatrogenic CJD can be prevented by limiting patient exposure to potentially infectious sources as mentioned above. Prevention of vCJD relies on monitoring livestock for possible infection. The American Red Cross does not accept blood donations from persons with a family history of CJD or with a history of dural grafts or pituitary-derived growth hormone injections.

An international referral and database for CJD is available at <http://www.cjdsurveillance.com>.

Bardelli M et al. A bispecific immunotweezer prevents soluble PrP oligomers and abolishes prion toxicity. *PLoS Pathog.* 2018;14:e1007335. [PMID: 30273408]

Houston F et al. Animal prion diseases: the risks to human health. *Brain Pathol.* 2019;29:248. [PMID: 30588682]

Tee BL et al. Prion diseases. *Neurol Clin.* 2018;36:865. [PMID: 30366560]

7. Progressive Multifocal Leukoencephalopathy (PML)

PML is a rare demyelinating CNS disorder caused by the reactivation of two polyoma viruses, the **JC virus** (John Cunningham virus or JCV) and, less commonly, the **BK virus** (associated with nephropathy). The JC virus usually causes its primary infection during childhood with about 80% of adults typically being seropositive. The virus remains latent in the kidneys, lymphoid tissues, epithelial cells, peripheral blood leukocytes, bone marrow, and possibly brain until reactivation occurs and symptoms become evident. This reactivation is usually seen in adults with impaired cell-mediated immunity, especially AIDS patients (5–10% of whom develop PML), as well as those with idiopathic CD4 lymphopenia syndrome. It is also reported among those with lymphoproliferative and myeloproliferative disorders; in those with granulomatous, inflammatory, and rheumatic diseases (systemic lupus erythematosus and rheumatoid arthritis in particular); in those who have undergone solid and hematopoietic cell transplantation; and occasionally in those who have other medical states, including cirrhosis and kidney disease. Diagnostic criteria that use clinical, imaging, pathologic, and virologic manifestations of JCV are available from the American Academy of Neurology.

Medication-associated PML is described with the use of natalizumab, rituximab, infliximab, alemtuzumab, azathioprine with corticosteroids, cyclophosphamide, and mycophenolate mofetil. Natalizumab, a monoclonal antibody used in the treatment of multiple sclerosis, is associated with the risk of PML developing in 4 per 1000 treated patients, with the rate increasing with duration of therapy. The risk of clinical PML appears to increase up to 36 months of therapy and levels off thereafter. The mean interval between use of the drug to the diagnosis of PML is 5.5 months. JCV is detected in the CSF of up to one-half of all patients treated with natalizumab. An immune reconstitution inflammatory state (IRIS) may follow cessation of natalizumab or other monoclonal antibody therapy, although the JCV presence and the residual neurologic deficits may not clear for years after therapy is stopped. The risk of developing PML associated with rituximab is at least 1 in 25,000 exposed patients with cases reported in various autoimmune conditions treated with rituximab (systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis). Although the exact relationship between latent JCV and frank PML remains unclear, higher JC viral loads are detected among patients who are immunosuppressed and among those who have HIV infection with lower CD4 cell counts.

► Clinical Findings

A. Symptoms and Signs

JCV causes lytic infection of oligodendrocytes in the white matter and symptoms presenting subacutely reflect the diverse areas of CNS involvement. Symptoms include altered mental status, aphasia, ataxia, hemiparesis or hemiplegia, and visual field disturbances. Seizures occur in about 18%. Involvement of cranial nerves and the cervical spine is rare.

B. Laboratory Findings

Quantitative PCR for JCV in CSF is used for diagnosis in patients with compatible clinical and radiologic findings. Persistent JC viremia and increasing urinary JCV DNA may be predictive of PML. An anti-JCV IgG was higher 6 months before diagnosis but was not predictive of PML in a cohort of people living with HIV infection.

C. Imaging

MRI of the brain shows multifocal areas of white matter demyelination without mass effect or, usually, contrast enhancement. These findings may not be distinguishable from IRIS. Increased uptake of methionine with concomitant decreased uptake of fluorodeoxyglucose in positron emission tomography may be helpful for diagnosis. In people living with HIV, a syndrome of cerebellar degeneration is described. Case reports attest to the variability of MRI findings and one should not rely on them solely for diagnosis.

► Treatment & Prevention

Limiting the immunosuppressed state without inducing an IRIS represents the mainstay of therapy for HIV-associated

PML. Treatment of HIV with ART reduces the incidence of PML, improves the clinical symptoms, reverses some of the radiographic abnormalities, and improves the 1-year mortality rate, regardless of baseline CD4 cell count. Immune recovery can induce worsening of the clinical picture in a small number of cases. Immune reconstitution syndromes do not alter mortality but are associated with a form of PML called **non-determined leukoencephalopathy** associated with a chemokine polymorphism. Significant neurologic sequelae to PML infections are the rule and deficits may persist for years.

Decreasing immunosuppression in patients without HIV but with PML (eg, patients with multiple sclerosis or those who have undergone transplant) is also important. Cidofovir may be beneficial in non-HIV-related cases, while corticosteroids may be useful with immune reconstitution. Because the JCV infects cells through serotonin receptors, some clinicians recommend the use of risperidone and mirtazapine. Anecdotal reports show that premature stopping of natalizumab in multiple sclerosis may itself lead to IRIS states. Plasma exchange, which theoretically reduces the plasma level of agents associated with PML, may be useful in natalizumab-associated PML but is associated with a high risk of IRIS. In patients post-kidney transplantation, a preinduction regimen with IVIG and rituximab and transplantation with lymphocyte-depleted cells appears to reduce the risk of PML. Titers of JC antibody are not shown to significantly increase prior to clinical onset of PML in patients who have undergone solid organ transplantation.

More recently, programmed cell death protein (PD-1) inhibitor therapy (also known as “immune checkpoint inhibitor”) is being evaluated for use in PML. The PD-1 inhibitor pembrolizumab reduced JC viral load and increases CD4+ and CD8+ activity against the virus in a preliminary set of eight patients with PML with different predisposing conditions. In addition, allogeneic BK virus-specific T cells are useful in lowering JC viral load.

Beck ES et al. Checkpoint inhibitors for the treatment of JC virus-related progressive multifocal leukoencephalopathy. *Curr Opin Virol.* 2020;40:19. [PMID: 32279025]

Cortese I et al. Pembrolizumab treatment for progressive multifocal leukoencephalopathy. *N Engl J Med.* 2019;380:1597. [PMID: 30969503]

Muftuoglu M et al. Allogeneic BK virus-specific T cells for progressive multifocal leukoencephalopathy. *N Engl J Med.* 2018;379:1443. [PMID: 30304652]

8. Human T-Cell Lymphotropic Virus (HTLV)

HTLV-1 and -2 are retroviruses that infect CD4 and CD8 T cells, respectively, where they persist as a lifelong latent infection. HTLV-1 currently infects approximately 20 million individuals worldwide. It is endemic to many regions in the world including southern Japan, the Caribbean, much of sub-Saharan Africa, South America, Eastern Europe, and Oceania. The Caribbean basin and southwestern Japan show the highest prevalence of infection (4–37%). Conversely, HTLV-2 is mainly found in native populations of South (1–58%), Central (8–10%), and North America

(2–13%) as well as African pygmy tribes. In some areas of Africa (eg, Malawi), HTLV-2 seroprevalence is higher than HTLV-1 seroprevalence.

In the United States, studies done in blood donors show a seroprevalence of HTLV-1 of 0.005% and HTLV-2 of 0.014%, a decline since the early 1990s. The virus is transmitted horizontally (sex), vertically (intrauterine, peripartum, and prolonged breastfeeding), and parenterally (injection drug use and blood transfusion). Hence, a higher prevalence is seen among injection drug users. Coinfection with HIV-1 occurs (in less than 5% in a series from Spain) but is often underrecognized. Transmission via organ transplant has been reported. Disease may flare when biologic agents are used for rheumatoid conditions. HTLV-1 infection is associated with **HTLV-1 adult T-cell lymphoma/leukemia (ATL)** and **HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP)**. In contrast, HTLV-2 is significantly less pathogenic, with few reported cases of HAM/TSP as well as other neurologic manifestations. The causative association of HTLV-1 with ATL, attributed to the virally encoded oncoprotein *tax*, is well established.

► Clinical Findings

A. Symptoms and Signs

The lifetime risk of developing ATL among HTLV-1 seropositive persons is estimated to be 3% in women and 7% in men, with an incubation period of at least 15 years. The mean age at diagnosis of ATL is 40–50 years in Central and South America and 60 years in Japan.

ATL clinical syndromes may be classified as chronic, acute (leukemic), smoldering, or lymphomatous. A primary cutaneous tumor is also described (with appearance ranging from papular lesions to exfoliative erythroderma) and shows a worse prognosis compared with the smoldering type. Clinical features of ATL include diffuse lymphadenopathy, maculopapular skin lesions that may evolve into erythroderma, periodontitis, a bronchoalveolar disorder, organomegaly, lytic bone lesions, and hypercalcemia. Opportunistic infections, such as *P jirovecii* pneumonia and cryptococcal meningitis, are common.

HAM/TSP, associated with both HTLV-1 and HTLV-2, develops in 0.3–4% of seropositive individuals and is more common in women and in older individuals. A chronic inflammation of the CNS and spinal cord leads to intense and progressive motor weakness and symmetric spastic paraparesis, bilateral facial palsies, cognitive impairment, falls, nociceptive low back pain, and paraplegia with hyperreflexia. Bladder and sexual disorders (eg, dyspareunia, erectile dysfunction), sensory disturbances, and constipation are also common. Both viruses can also induce motor abnormalities, such as leg weakness, impaired tandem walk, and vibration sense, without overt HTLV-associated myelopathy.

Studies from Brazil show that a subset of chronically inflamed patients with HTLV-1 infections may be asymptomatic and are recognized as having an “intermediate syndrome” that may progress to full blown myelopathy.

HTLV-1 seropositivity is associated with an increased risk of tuberculosis, *Strongyloides stercoralis* hyperinfection, crusted scabies, and infective dermatitis. Inflammatory states associated with HTLV-1 infection include arthropathy, recurrent facial palsies, polymyositis, uveitis, and sicca, but inconsistently Sjögren syndrome, vasculitis, cryoglobulinemia, infiltrative pneumonitis, and ichthyosis. Bronchioloalveolar carcinoma is increased in frequency in the presence of HTLV-1.

HTLV-2 appears to cause a myelopathy that is milder and slower to progress than HAM. All-cause and cancer mortality are higher among HTLV-2 seropositive patients.

HTLV-1/HIV coinfection is associated both with higher CD4 cell counts and a higher risk of HAM.

B. Laboratory Findings

The peripheral smear can show atypical lymphoid cells with basophilic cytoplasm and convoluted nuclei (flower cells). The diagnostic standard is evidence of clonal integration of the proviral DNA genome into tumor cell. The identification of HTLV-1 antibodies supports the diagnosis. Serum neopterin levels may indicate disease activity. An HTLV-1 provirus load in peripheral blood mononuclear cells and CSF cells and an HTLV-1 mRNA load are proposed as markers of HAM risk and progression. HTLV positivity is associated with erythrocytosis, lymphocytosis (HTLV-2), and thrombocytosis (HTLV-1).

► Treatment, Prevention, & Prognosis

No vaccine or antiviral therapy currently exists for the prevention and treatment of HTLV infections.

Management of ATL consists mainly of chemotherapy (such as CHOP and EPOCH regimens), followed by allogeneic stem cell transplantation. Immunotherapies are increasingly used, including monoclonal antibodies (eg, the anti-CCR4 inhibitor mogamulizumab, anti-CD25 agents), SYK/JAK (spleen tyrosine kinase/Janus kinase) inhibitors (eg, cerdulatinib and ruxolitinib), and PD-1/immune checkpoint inhibitors (eg, nivolumab). A chemotherapy regimen in Japan using eight different agents shows a higher response rate than traditional biweekly CHOP (40% vs 25%). A clinical trial is underway evaluating lenalidomide plus EPOCH (NCT04301076). Combination therapy with interferon-alpha is used with success. Prophylaxis against infections is needed in ATL because patients show a profound immunodeficiency. Patients who are coinfected with HIV-1 and HTLV reportedly do respond to ART.

HAM is treated with a variety of immune-modulating agents (including corticosteroids) without consistent results. Modalities of therapy, none of which are uniformly accepted as a mainstay, include combination therapy with the antiretroviral raltegravir alone or in combination with zidovudine; interferon-alpha; and a combination of prednisolone, pegylated interferon, and sodium valproate; pentoxifylline, cyclosporine, and the retinoid tamibarotene. Small, uncontrolled studies suggest plasmapheresis results in improvement in gait and sensory disturbance among some patients and improvement in muscle pain

with pulsed methylprednisolone. Clinical trials are underway evaluating novel therapies such as the monoclonal antibody mogamulizumab (KW-0761) and tamibarotene (AM80H, also known as retinobenzoic acid).

Screening of the blood supply for HTLV-1 is required in the United States. There is significant cross-reactivity between HTLV-1 and HTLV-2 by serologic studies, but PCR can distinguish the two. Improved assays to screen organ donors for HTLV-1 and -2 infections are needed, although such screening is not currently required. Antenatal screening and avoiding breastfeeding (where the virus can be transmitted) are also important preventive measures.

- Champs APS. Cognitive impairment in HTLV-1-associated myelopathy, proviral load and inflammatory markers. *Int J Infect Dis.* 2019;84:121. [PMID: 31085316]
- Hirons A et al. Human T-cell lymphotropic virus type-1: a life-long persistent infection, yet never truly silent. *Lancet Infect Dis.* 2021;21:e2. [PMID: 32986997]
- Kannagi M et al. Impact of host immunity on HTLV-1 pathogenesis: potential of Tax-targeted immunotherapy against ATL. *Retrovirology.* 2019;16:23. [PMID: 31438973]
- Keikha M et al. Molecular targeting of PD-1 signaling pathway as a novel therapeutic approach in HTLV-1 infection. *Microb Pathog.* 2020;144:104198. [PMID: 32283259]
- Marino-Merlo F et al. Antiretroviral therapy in HTLV-1 infection: an updated overview. *Pathogens.* 2020;9:342. [PMID: 32369988]

VIRAL HEMORRHAGIC FEVERS

1. Ebola Viral Disease (EVD)



ESSENTIALS OF DIAGNOSIS

- ▶ Early stage EVD: a nonspecific febrile illness.
- ▶ Later stage EVD: severe gastrointestinal symptoms, then neurologic symptoms and hypovolemic shock.
- ▶ Hemorrhagic manifestations are late-stage manifestations.
- ▶ Uveitis is prominent.
- ▶ Travel and contact history from an Ebola-affected country raise suspicion.
- ▶ Virus is detected via RT-PCR.

► General Considerations

Genus *Ebolavirus* is a single-stranded RNA virus in the Filoviridae family. Four different species of *Ebolavirus* have been identified to cause human disease. Fruit bats are possible reservoir for *Ebolavirus*. Zoonotic transmission to humans occurs via contact with the reservoir or an infected primate. *Ebolavirus* can continue to be transmitted among humans who have direct contact with infected body fluids. To acquire EVD, the virus must enter the body via mucous membranes, nonintact skin, sexual intercourse,

breastfeeding, or needlesticks. Traditional burial practices in some African communities (which entail considerable contact with the corpse) and unprotected direct care of persons with EVD are associated with highest transmission risk. *Ebolavirus* has been detected in semen up to 9 months after recovery from infection.

EVD has a 2–21-day incubation period. Prior to manifestation of symptoms, *Ebolavirus* is not transmissible. Even at symptom onset, the risk of transmission is low but increases over time.

The first Ebola outbreak occurred in 1976 as a simultaneous epidemic in the Democratic Republic of Congo and South Sudan. Subsequent outbreaks were confined to the Democratic Republic of Congo, Uganda, and Sudan until March 2014 when the first Ebola case in West Africa was identified in Guinea. *Zaire ebolavirus* was the associated species. This Ebola outbreak grew to be larger than all prior Ebola outbreaks combined. The number of EVD cases spread rapidly; there were at least 10 affected countries, especially Guinea, Liberia, and Sierra Leone. Many cases and deaths in these countries occurred among health care workers. In the United States, 11 persons were treated for Ebola. Most were health care workers who were evacuated to the United States and 4 patients were diagnosed in the United States. In total, 39 outbreaks of Ebola have occurred since 1976, mostly in Africa.

► Clinical Findings

A. Symptoms and Signs

At symptom onset, early-stage EVD most typically presents as a nonspecific febrile illness. Along with fever, patients tend to experience headache, weakness, dizziness, malaise, fatigue, myalgia, and arthralgia. After 3–5 days, patients with later stage EVD may develop abdominal pain, severe nausea, vomiting, and diarrhea accompanying the febrile illness. This stage of the illness may continue for a week during which time neurologic symptoms gain prominence. Encephalitis is commonly observed and manifested as confusion, slowed cognition, agitation, and occasional seizures. Hypovolemic shock develops in most patients, but hemorrhagic manifestations (gastrointestinal bleeding, diffuse mucosal bleeding, conjunctival bleeding) develop in only 1–5% of patients. Respiratory symptoms are not typical for EVD, although interstitial pneumonia and respiratory failure are reported.

B. Laboratory Findings

During the first few days of symptoms, diagnosis may be made via several modalities, including antigen-capture ELISA, IgM ELISA, RT-PCR, or virus isolation. Blood samples obtained within the first 3 days of illness and tested by RT-PCR should be repeated if results are negative and clinical symptoms and signs persist. RNA levels peak a median of 7 days after illness onset. Later in the disease course or after recovery, IgM and IgG serologic tests may be sent. After about 10 days, IgM antibodies begin to develop, and, after approximately 2 weeks, an IgG antibody response develops. Postmortem diagnosis may be made by using immunohistochemistry, RT-PCR, or virus isolation.

Given that filoviruses infect dendritic cells and then hepatocytes and renal cortical cells, laboratory findings typically include a low platelet count (and a thrombotic thrombocytopenic purpura syndrome has been postulated with the probable cause multifactorial), leukopenia, and transaminitis (aspartate aminotransferase [AST] greater than alanine aminotransferase [ALT]). As nonspecific symptoms progress to a severe systemic inflammatory response, coagulopathy with evidence of platelet dysfunction and disseminated intravascular coagulopathy (DIC) often develops. Whether DIC is a common cause of bleeding has not yet been firmly established because clinical measurements of fibrinogen, prothrombin time, fibrin split products, and platelets are not routinely taken in the communities where most outbreaks have occurred. Additional observed laboratory abnormalities include hypoalbuminemia, electrolytes imbalance, and increased serum creatinine level. Elevated blood urea nitrogen, AST, and creatinine upon presentation are associated with higher mortality.

Differential Diagnosis

The differential diagnosis varies with the stage of illness. Early-stage EVD is commonly mistaken for malaria, typhoid, and other viral illnesses. As gastrointestinal symptoms develop, health providers should also consider viral hepatitis, toxins, leptospirosis, and rickettsial diseases. In later stage EVD, bacterial, viral, and parasitic illnesses, including cholera and, in children, rotavirus infection can present with severe gastroenteritis and shock. Encephalitis must be differentiated from the confusion associated with uremia. Hemorrhagic manifestations raise suspicion for EVD but could be due to leukemia, thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, or disseminated intravascular coagulation. Travel and contact history are crucial when considering the differential diagnosis in areas where Ebola is not endemic.

Complications

Hypovolemic shock and multiorgan failure are the most common complications of EVD. Hemorrhage can occur in late stages. Rhabdomyolysis is reported frequently and may explain many of the associated laboratory abnormalities. Coinfections with malaria or bacteria (or both) are important considerations and can occur before presentation and during treatment of EVD. The virus is known to persist in immunologically privileged sites, such as the CNS, eye, and testes; however, viral relapse is uncommon. Post-EVD musculoskeletal pain, headache, auditory symptoms including hearing loss, and ocular symptoms (uveitis being the most common ocular finding) may develop. EVD survivors exhibit high rates of neuropsychological long-term sequelae including depression, anxiety, and posttraumatic stress disorder.

Treatment

Treatment is supportive. Several studies have shown that intravenous fluids can reduce the mortality rates to less than 50%. Despite the wide availability of oral rehydration

salts, mortality approximates 70% in endemic areas. In these studies, the amount of intravenous fluid replacement was relatively less than what would be used in countries with more developed health systems. Among patients treated in the United States or Europe, almost all received intravenous fluids, electrolyte supplementation, and empiric antibiotic therapy. Invasive or noninvasive mechanical ventilation and continuous renal replacement therapy are necessary in many cases. This increased level of intervention likely contributed to the decreased mortality (19%) among these patients. The use of individual air-conditioned biosecure cubicles is preferred to the burdensome protective equipment used during the 2014 West African outbreaks and allows for more time spent with patients.

There are no approved medications for the treatment of EVD. Administration of convalescent plasma does not result in improved survival. Several medications have advanced to clinical trials; however, some trials were terminated due to low enrollment or lack of efficacy. Monoclonal antibodies that have been tested include mAb114 (a monoclonal antibody isolated from a survivor of the 1995 outbreak in the Democratic Republic of the Congo), ZMapp (a cocktail of three chimeric monoclonal antibodies against *Z ebolavirus*), and REGN-EB3 (another cocktail of three monoclonal antibodies against *Z ebolavirus*). ZMapp showed some therapeutic benefit, but many of these patients received multiple agents and were not part of randomized controlled trials. The PREVAIL II study evaluated ZMapp for treatment of EVD and found it to be safe and well tolerated but failed to establish efficacy due to low enrollment numbers. REGN-EB3 is given as a single dose, does not require freezing, and shows efficacy in nonhuman primates, including reduction in mortality. Starting in November 2018, the Pamoja Tulinde Maisha (PALM) trial enrolled 681 Congolese patients to receive one of four investigational drugs: mAb114, ZMapp, REGN-EB3, or remdesivir (GS-5734; a novel nucleotide analog prodrug). The trial was stopped early because preliminary results from 499 patients showed that those taking REGN-EB3 or mAb114 had a greater chance of survival than patients who received the other two medications (mortality with mAb-114 or REGN-EB3 was 35.1–33.5% compared to 49.7–53.1% mortality for those who received ZMapp or remdesivir). REGN-EB3 (marketed as Inmazeb) was approved by the FDA on October 14, 2020.

In the 2018 outbreak in the Democratic Republic of the Congo, the two antivirals used were remdesivir and the RNA-dependent RNA polymerase inhibitor favipiravir. Mathematical models show a high likelihood of efficacy for both agents against EVD if given within 3–4 days of infection, and the efficacy of remdesivir is theoretically 100% while that of favipiravir is 60%. Although both agents were effective in nonhuman primates and one study in humans found favipiravir to be effective in patients with low to moderate viremia, a 2019 trial of favipiravir in 99 participants found no difference in mortality for persons with low or high viral loads compared to historical controls.

Aside from supportive treatment and experimental therapeutics, patients typically receive empiric antimalarial agents in endemic areas and broad-spectrum antibiotics.

► Prognosis

Children under 5 years of age and adults older than 40 have a high risk of death from EVD. Pregnancy is a risk factor for severe illness and death. In the 2014–2016 outbreak, the average maternal mortality was 86%. Immunosuppressed patients had shorter incubation time, rapid progression of disease, and poor outcomes. A higher baseline viral load was a strong predictor of mortality. In general, poor overall medical care confers a poor prognosis. Among survivors, protective antibodies persist for at least 10 years.

► Prevention

Risk reduction should focus on preventing wildlife to human transmission and reducing human to human transmission by surveillance, early detection and isolation of cases, contact tracing, containment measures (disinfection, hygiene, and sanitation), strict droplet and contact precautions in health care setting, and reduction of sexual transmission in Ebola survivors. The WHO recommends that men avoid sexual activity or use barrier protection during intercourse for 12 months from onset of symptoms or until their semen tests negative twice for Ebola virus.

There are two Ebola vaccines being used in the ongoing epidemic in the Democratic Republic of the Congo. The recombinant vesicular stomatitis virus (rVSV)-based vaccine expressing *Z ebolavirus* (ZEBOV) glycoprotein is found to be highly effective in disease prevention after 10 days from receiving the vaccine. Side effects, such as fever, myalgia, chills, fatigue, headaches, and oligoarthritis, developed in most of the persons who received the vaccine. rVSV-ZEBOV (marketed as Ervebo) showed promising results in phase 3 clinical trials (most study participants had persistent antibody levels at 1 year; NCT02503202). In addition, it was tested in a clinical trial conducted in Guinea during the 2014–16 Ebola outbreak in West Africa and was found to offer a high level of protection against Ebola (100% efficacy). *rVSV-ZEBOV is the only Ebola vaccine candidate that has so far been able to demonstrate clinical effectiveness.* It was approved by the European Medicines Agency (EMA) on November 11, 2019 and by the US FDA on December 19, 2019. The adenovirus/vaccinia virus vector vaccine was also deployed in the outbreak in the Democratic Republic of the Congo, which began in 2018; EMA approval for this vaccine is pending. The adenovirus/vaccinia virus vector vaccine is actually a two-dose series of two different vaccines, Ad26.ZEBOV (replication-incompetent recombinant adenovirus 26 expressing the ZEBOV [Mayinga strain] glycoprotein) and MVA-BN-Filo (a nonreplicating modified vaccinia Ankara-Bavarian Nordic virus vector expressing the glycoproteins of Zaire and Sudan ebolaviruses, Marburg virus, and the nucleoprotein of Tai Forest virus), given about 6 weeks apart (NCT03140774). This vaccine is being tested in a clinical trial in the Democratic Republic of the Congo at a dose that has shown 100% protective efficacy in nonhuman

primate studies and that is well tolerated and immunogenic in extensive phase 1–2 trials. Nevertheless, concerns remain about public acceptance of an investigational two-dose vaccine when an approved one-dose vaccine (rVSV-ZEBOV) is already available.

There are over 12 other Ebola vaccines in various stages of clinical testing, including a recombinant Ebola virus glycoprotein nanoparticle formulated with a saponin-based Matrix-M adjuvant.

Risk stratification may be useful in deciding when and to whom to administer antiviral postexposure prophylaxis. A high-risk exposure is defined as penetrating sharps injury from used device or through contaminated gloves or clothing, direct contact with an infected patient (alive or deceased) or their bodily fluids with broken skin or mucous membranes such as eyes, nose, or mouth. The rVSV-ZEBOV vaccine was used in the setting of postexposure prophylaxis among health care workers and found to be effective, but the evidence is limited to case series. The vaccine-mediated immunity requires an average of 10 days to develop and might not be fast enough in certain cases to prevent infection.

Ongoing studies focus on isolation of cross-reactive monoclonal antibodies across Ebola virus species. The use of different preparations of combination monoclonal antibodies (Zmapp and MIL-77E) as postexposure prophylaxis during the West African outbreak failed to show statistical significance, and the conclusion was that the benefit was modest, at best. Newer forms of monoclonal antibodies include virus-like particles (VLP), mucin-deleted glycoproteins, and bispecific binding proteins (which bind Ebola proteins as well as those of related viruses such as the Sudan virus). The use of antiviral agents in postexposure prophylaxis is another alternative that, to date, also shows no clear survival benefit. The agent brincidofovir, for example, was not studied further because of inadequate sample size in Liberia.

► When to Admit

Persons living in or returning from a country with high rates of Ebola transmission should be monitored for 21 days and admitted to a health care facility when symptoms meeting the WHO case definition of a suspected EVD case develop, in accordance with the screening protocol designated by the respective country's governmental health decision-making body.

Callaway E. 'Make Ebola a thing of the past': first vaccine against deadly virus approved. *Nature*. 2019;575:425. [PMID: 31745354]
Centers for Disease Control and Prevention (CDC). MMWR Ebola reports. https://www.cdc.gov/mmwr/ebola_reports.html
Chertow DS. Understanding long-term effects of Ebola virus disease. *Nat Med*. 2019;25:714. [PMID: 31036880]
Fischer WA 2nd et al. Ebola virus disease: an update on post-exposure prophylaxis. *Lancet Infect Dis*. 2018;18:e183. [PMID: 29153266]
Fries L. A randomized, blinded, dose-ranging trial of an Ebola virus glycoprotein (EBOV GP) nanoparticle vaccine with matrix-M adjuvant in healthy adults. *J Infect Dis*. 2020; 222:572. [PMID: 31603201]

Ilunga Kalenga O et al. The ongoing Ebola epidemic in the Democratic Republic of Congo, 2018–2019. *N Engl J Med.* 2019;381:373. [PMID: 31141654]
Kuehn B. Early success in Ebola trial. *JAMA.* 2019;322:1441. [PMID: 31613352]

2. Other Hemorrhagic Fevers

This diverse group of illnesses results from infection with one of several single-stranded RNA viruses (members of the families Arenaviridae, Bunyaviridae, Filoviridae, and Flaviviridae). Flaviviruses, such as the pathogens causing dengue and yellow fever, and Filoviridae, causing EVD, are discussed in separate sections.

Lassa fever is a rodent-associated disease caused by an Old-World *arenavirus*. Rodents shed the virus in urine and droppings and transmit the virus to humans either by direct contact with these materials, ingestion, or inhalation of aerosolized particles. Lassa fever is mostly endemic in West Africa, where 100,000 to 300,000 cases and 5000 deaths are seen annually. Case fatality rates in hospitalized patients in West Africa are up to 50%. Other arenaviruses include the Junin virus (cause of Argentinian hemorrhagic fever) and the Lujo virus. Lujo virus was first described in 2008 in Zambia where it caused a small cluster of nosocomial infections.

The bunyavirus hemorrhagic fevers include hantaviruses (discussed separately), Crimean Congo hemorrhagic fever, Rift Valley fever, and several newly emerging viruses such as the one that causes severe fever with thrombocytopenia syndrome.

Crimean Congo hemorrhagic fever (CCHF) is a disease transmitted from ticks and livestock. Human-to-human transmission can occur in the community or hospital setting by contact with infected body secretions. The geographic distribution is widespread with cases reported from Africa, Asia, the Middle East, and Eastern Europe, with increased incidence recently in the East Mediterranean region. Butchers and slaughterhouse workers in southeastern Iran are at high risk for infection with the CCHF pathogen.

Rift Valley fever is transmitted from livestock animals, infected mosquitoes, and flies. To date, there is no human-to-human transmission. Risk factors for acquiring Rift Valley fever include working with abortive animal tissue; slaughtering, skinning, or sheltering animals; and drinking unpasteurized milk. Rift Valley fever causes outbreaks in Africa and the Arabian Peninsula.

A new bunyavirus was identified in 2009 in central and northeastern China and was named for its symptoms: **severe fever with thrombocytopenia syndrome (SFTS)** virus. SFTS is transmitted by tick bite (Ixodidae family, including the tick *Haemaphysalis longicornis*, which is found in Asia as well as among animals [rarely humans] in the eastern United States). It may also be transmitted between humans through direct contact with infected blood or secretions. Another virus (**Heartland virus**), identified in the United States, is similar to the SFTS virus. Transmission occurs via the Lone Star tick (*Amblyomma americanum*). The virus appears to be amplified in deer

and raccoons. In the United States, most cases are reported from the Midwest and southern states.

Clinical Findings

A. Symptoms and Signs

The incubation period varies between species, ranging from 2 to 21 days. The clinical symptoms in the early phase of a viral hemorrhagic fever are indistinguishable from other viral illnesses. Due to lack of specific symptoms on presentation, viral hemorrhagic fevers are an important cause to consider in fever of unknown origin in children in endemic areas. The late phase is more specific and is characterized by organ failure, altered mental status, and hemorrhage. Exanthems and mucosal lesions can occur.

In advanced stages, significant edema, pleural effusion, and fewer hemorrhagic manifestations compared with EVD can develop in patients with Lassa fever and Lujo virus infection. Hearing loss in various degrees is the most common complication of Lassa fever infection. Mortality in pregnant patients during the third trimester and fetal mortality are very high.

CCHF has more prominent hemorrhagic manifestations. Patients have red eyes, flushed face, red throat, and petechiae that progress to severe uncontrollable bleeding. Severe headaches are common in CCHF and correlate with the severity of vascular damage, vasodilatation, and cytokine release.

Rift Valley fever disease can present with three distinct syndromes: (1) ocular disease; retinitis is the most common complication and permanent vision loss develops in 1–10% of patients; (2) meningoencephalitis occurs in less than 1% of cases; these patients have headache, coma, or seizures 1–4 weeks after initial symptoms and a low mortality but a high morbidity with neurologic deficits that can be severe; and (3) hemorrhagic fever; patients present 2–4 days after illness and show evidence of severe liver impairment and later hemorrhages; the hemorrhagic state occurs in less than 1% of patients, but the case-fatality ratio of such patients reaches about 50%.

B. Laboratory Findings

Laboratory features usually include thrombocytopenia, leukopenia (although with Lassa fever leukocytosis is noted), anemia, elevated liver biochemical tests, and abnormalities consistent with disseminated intravascular coagulation.

Special care should be taken for handling clinical specimens of suspected cases. Laboratory personnel should be warned about the diagnostic suspicion, and the CDC must be contacted for guidance. The diagnosis may be made by antigen detection (by ELISA), culture of the virus (the “gold standard” for Lassa virus diagnosis), PCR, or demonstration of a fourfold rise in antibody titer. CCHF is best diagnosed with an IgM serology, although IgG ELISA or immunofluorescence and quantitative RT-PCR are nearly as effective. Isolation of the viruses in culture requires a biosafety level 4 laboratory. Serologic assays are attendant with early false-negative and late false-positive assays.

► Differential Diagnosis

The differential diagnosis for hemorrhagic fever includes meningococcemia or other septicemias, rickettsial infection, dengue, typhoid fever, and malaria. SFTS differential diagnosis includes anaplasmosis, hemorrhagic fever with renal syndrome, or leptospirosis. The likelihood of acquiring hemorrhagic fevers among travelers is low.

► Treatment & Prevention

Patients should be placed in private rooms with standard contact and droplet precautions. Barrier precautions to prevent contamination of skin or mucous membranes should also be adopted by health care providers. Airborne precautions should be considered in patients with significant pulmonary involvement or undergoing procedures that stimulate cough.

Supportive care is the mainstay of therapy. There is no approved antiviral medication, but ribavirin is shown to be effective *in vitro* and *in vivo* against Lassa virus. Early diagnosis and management can reduce mortality.

Postexposure prophylaxis with ribavirin in the management CCHF appears to be effective; however, little data exist to support its efficacy for Lassa fever and other arenaviruses. The antitrypanosomal agent suramin may be effective against the Rift Valley fever virus. Sorafenib, a tyrosine kinase inhibitor approved for treatment of renal cell and hepatocellular carcinoma, has antiviral activity against Rift Valley fever virus. A combination of monoclonal antibodies that cross-react with the glycoproteins of Lassa virus has been tested in macaques with promising results.

An inactivated vaccine is available for Rift Valley fever but is not licensed and is not commercially available. There are no vaccines approved for other viruses causing viral hemorrhagic fever. Several vaccines have been developed for Lassa virus but only one has entered clinical trials. A one-dose vaccine for Lassa virus that consists of a measles vector simultaneously expressing LASV glycoprotein and nucleoprotein was successfully tested in monkeys and is currently a phase 1 clinical trial involving 60 human participants (NCT04055454).

The main method of preventing Rift Valley fever is vaccination of susceptible livestock before outbreaks occur. Several vaccines have been developed for Rift Valley fever control in livestock, but only one, the Smithburn vaccine (a live attenuated virus), is produced commercially and used in East Africa. An inactivated vaccine has been developed for humans but is neither licensed nor commercially available.

► When to Admit

- Persons with symptoms of any hemorrhagic fever and who have been in possible endemic area should be isolated for diagnosis and symptomatic treatment.
- Isolation is particularly important because diseases due to some of these agents, such as Lassa virus, are highly transmissible to health care workers.

Mateo M et al. Vaccines inducing immunity to Lassa virus glycoprotein and nucleoprotein protect macaques after a single shot. *Sci Transl Med*. 2019;11:eaaw3163. [PMID: 31578242]
 Qi R et al. Severe fever with thrombocytopenia syndrome can masquerade as hemorrhagic fever with renal syndrome. *PLoS Negl Trop Dis*. 2019;13:e0007308. [PMID: 30925154]

Smith DR et al. Attenuation and efficacy of live-attenuated Rift Valley fever virus vaccine candidates in non-human primates. *PLoS Negl Trop Dis*. 2018;12:e0006474. [PMID: 29742102]
 Zakham F et al. Viral haemorrhagic fevers in the Middle East. *Rev Sci Tech*. 2019;38:185. [PMID: 31564731]

3. Dengue



- ▶ Incubation period 7–10 days.
- ▶ Sudden onset of high fever, chills, severe myalgias and arthralgias, headache, and retroorbital pain.
- ▶ Severe dengue is defined by the presence of plasma leakage, hemorrhage, or organ involvement.
- ▶ Signs of hemorrhage such as ecchymoses, gastrointestinal bleeding, and epistaxis appear later in the disease.

► General Considerations

Dengue virus belongs to the genus *Flavivirus* and has four distinct serotypes that can cause infection. Infection with one serotype does not confer immunity to the other serotypes. Dengue is transmitted primarily from human to human by the bite of the *Aedes* mosquito. Health care-associated transmission (needlestick or mucocutaneous exposure) and vertical transmission occur rarely. Transmission via bone marrow and solid organ transplant is also known to occur. WHO reports that dengue is currently endemic in 128 countries, mostly in tropical and subtropical regions with more than 3 billion persons at risk for infection. An estimated 100–400 million cases of dengue fever occur annually. Case numbers have increased over the last two decades; this surge of cases is associated with climatic factors, travel, and urbanization. Thus, along with malaria, *dengue is one of the two most common vector-borne diseases of humans*. Dengue is also the *second overall cause of a febrile illness (after malaria and excluding common upper respiratory viral infections) in travelers returning from developing countries*.

Most dengue cases occur in Asia (about 70% of cases) and Latin America. In 2019, high numbers of cases were reported in Bangladesh (greater than 101,000), Malaysia (greater than 131,000), Philippines (greater than 420,000), and Vietnam (greater than 320,000). In 2020, increasing case numbers were reported in Bangladesh, Brazil, Cook Islands, Ecuador, India, Indonesia, Maldives, Mauritania, Mayotte (France), Nepal, Singapore, Sri Lanka, Sudan, Thailand, Timor-Leste, and Yemen. As of October 20, 2020, Brazil, Paraguay, Bolivia, Argentina, and Malaysia have reported most dengue cases.

In the United States, even though dengue is endemic in Northern Mexico and the *Aedes* mosquito is common in the southern states, outbreaks are uncommon. Most cases occur in travelers, immigrants, or inhabitants of US territories that are endemic to the dengue virus. Puerto Rico experiences periodic large outbreaks, as did Hawaii in 2015 and 2016. As of November 9, 2020, 250 dengue cases were reported in United States (including 69 locally acquired cases reported in Florida; the remaining cases were travel-acquired) and 439 in US territories (primarily Puerto Rico).

The incubation period is usually 7–10 days. When the virus is introduced into susceptible populations, usually by viremic travelers from endemic countries, epidemic attack rates range from 50% to 70%.

► Clinical Findings

A. Symptoms and Signs

A history of travel to a dengue-endemic area within 14 days of symptom onset is helpful in establishing a diagnosis. Most infected patients are asymptomatic. Only 20% develop symptoms ranging from mild disease (dengue fever) to severe hemorrhagic fever to fatal shock (dengue shock syndrome). In 1997 the WHO classified symptomatic dengue into dengue fever, dengue hemorrhagic fever, and dengue shock syndrome. The 2009 WHO classification of dengue is the following: dengue without warning signs; dengue with warning signs; and severe dengue. This classification was criticized for lacking clarity and mixing distinct disease phenotypes within each category and was not adopted by all countries.

After the incubation period, the febrile phase begins abruptly with nonspecific symptoms, high fever, chills, facial flushing, malaise, retroorbital eye pain, generalized body pain, and arthralgia. Some patients might have maculopapular rash, sore throat, and conjunctival injection. Not all patients have all symptoms or fever. Mild hemorrhagic manifestations can be seen. Most of the patients will recover, and fever is usually cleared by day 8.

A subset of patients, especially those with suboptimally controlled type 2 diabetes, may progress to severe dengue, which is defined by the presence of plasma leakage, hemorrhage, or organ involvement. Hematocrit drop may be the earliest sign and an indicator of the severity of plasma leakage. Pleural effusion and ascites can develop and may be detected by lateral decubitus chest radiograph or ultrasound before clinical detection. Increasing liver size, persistent vomiting, and severe abdominal pain are indications of plasma leakage. Signs of hemorrhage such as ecchymoses, gastrointestinal bleeding, and epistaxis appear. Severe organ involvement may develop, such as hepatitis, encephalitis, and myocarditis.

Shock develops in patients when a critical volume of plasma is lost through leakage. Decrease in the level of consciousness, hypothermia, hypoperfusion resulting in metabolic acidosis, progressive organ impairment, and disseminated intravascular coagulation leading to severe hemorrhage should raise concern for shock. Acute kidney injury in dengue largely occurs with shock syndrome and shows a high mortality.

B. Laboratory Findings

Leukopenia is characteristic, and elevated transaminases are found frequently in dengue fever. Thrombocytopenia, fibrinolysis, and hemoconcentration occur more often in the hemorrhagic form of the disease. In other forms of disease, especially in children, anemia is more common. The erythrocyte sedimentation rate (ESR) is normal in most cases.

The nonspecific nature of the illness mandates laboratory verification for diagnosis, usually with IgM and IgG ELISAs after the febrile phase. Virus is recovered from the blood by PCR or detection of the specific viral protein NS1 by ELISA during the first few days of infection. Immunohistochemistry for antigen detection in tissue samples and dried blood spots can also be used. Thrombocytopenia and blood vessel fragility in remote settings can be assessed with a tourniquet test.

► Differential Diagnosis

Distinguishing between dengue and other causes of febrile illness in endemic areas is difficult. Fevers due to dengue are more often associated with neutropenia and thrombocytopenia and with myalgias, arthralgias/arthritis, and lethargy among adults. Chikungunya is more apt to develop a chronic arthritis. The arboviral encephalitides require additional epidemiologic information and serologic data to make the diagnosis. Influenza and malaria are easily confused early in disease, although the rhinitis and malaise should help distinguish influenza, and the cyclicity of fevers and presence of splenomegaly should suggest malaria.

► Complications

Usual complications include pneumonia, bone marrow failure, hepatitis, iritis, retinal hemorrhages and maculopathy, orchitis, and oophoritis. Neurologic complications (such as encephalitis, Guillain-Barré syndrome, phrenic neuropathy, subdural hematoma, cerebral vasculitis, and transverse myelitis) are less common. Acute disseminated encephalomyelitis has been linked with infection and the live dengue vaccine. Bacterial superinfection can occur. Oral complications include acute gingivitis, palatal bleeding, tongue plaques, xerostomia, and rarely osteonecrosis of the jaw.

Maternal infection poses a risk of hemorrhage in both the mother and the infant if infection occurs near term. Severe dengue is a risk factor for obstetric complications, cesarean delivery, fetal distress, and maternal morbidity.

► Treatment

There are no specific therapeutic options for the clinical management of dengue besides supportive care. Treatment entails the appropriate use of volume replacement, blood products, and vasopressors. Acetaminophen is recommended for analgesic and antipyretic treatment. NSAID usage should be minimized and preferably avoided to decrease the risk of gastritis and bleeding, particularly in patients with a predilection for hemorrhage or when there are abnormalities in platelets, liver function, or clotting factors.

Platelet counts do not usefully predict clinically significant bleeding. Platelet transfusions may be considered for

severe thrombocytopenia (less than 10,000/mcL [$10.0 \times 10^9/L$]) or when there is evidence of bleeding. However, benefit in the absence of bleeding may not be observed, and harm may be caused by delay in count recovery. Monitoring vital signs and blood volume may help in anticipating the complications of dengue hemorrhagic fever or shock syndrome.

Repurposed medications, such as chloroquine, statins, and balapiravir, have not shown clear therapeutic benefit. Research is focusing on monoclonal antibodies as a therapeutic option as well as medications, including peptide agents that target structural and nonstructural proteins of dengue virus essential to its replication.

► Prognosis

Although fatalities occur with severe disease, the estimated mortality (2.5% of severe cases) appears to be diminishing, likely due to improved recognition of the disease and wider availability of supportive treatment. Causes of death include hemorrhagic fever (seen with recurrent disease) and occasionally fulminant hepatitis. Thrombocytopenia and acute hepatitis are predictors of severe dengue and higher mortality. Acute kidney injury in dengue shock syndrome portends poor prognosis. In general, the more severe forms of disease (hemorrhagic fever and shock) occur more often in Asia than in the Americas. Comorbidities of cardiovascular disease, diabetes, stroke, pulmonary disease, kidney disease, and older age are associated with more severe dengue.

► Prevention

Preventive measures should be encouraged, such as control of mosquitoes by screening and insect repellents including long-lasting insecticides, particularly during early morning and late afternoon exposures. Screening blood transfusions for dengue is important, especially in endemic areas.

Dengvaxia (CYD-TDV), a recombinant, live, attenuated, tetravalent dengue vaccine, is FDA approved for children 9–16 years old with previous history of dengue infection and who live in endemic areas. It was first licensed in 2015 and is approved in more than 20 countries. Trials evaluating the efficacy of this vaccine reported overall 56% efficacy; however, efficacy was lower in younger age groups, seronegative individuals at the time of vaccination, and those infected with dengue serotype 2. The vaccine is given as a 0-, 6-, and 12-month series. Serious side effects were no more common than in placebo recipients. Vaccination is indicated for those between ages 9 and 45 years. However, Dengvaxia carries an increased risk of severe dengue in those who experience their first natural dengue infection after vaccination (those who were seronegative at the time of vaccination). Thus, the WHO recommends limiting the vaccine to those who have had at least one dengue infection prior to vaccination and, for countries considering using Dengvaxia as part of their dengue control program, recommends pre-vaccination screening using dengue serology. Pregnant women and immunosuppressed persons should not be vaccinated. Another tetravalent dengue vaccine, a two-dose TAK-003,

is currently in phase 3 clinical trials and has shown promising results (73.3% efficacy; NCT02747927).

Since 2011, researchers have been injecting a bacterium that blocks mosquitos' ability to transmit viruses (such as dengue and *Wolbachia pipiensis*) into the eggs of *Aedes aegypti* mosquitoes. In some study areas, as much as a 76% reduction in the rate of dengue has been observed.

Biswas S et al; TIDES Study Group. Efficacy of a tetravalent dengue vaccine in healthy children and adolescents. *N Engl J Med.* 2019;381:2009. [PMID: 31693803]

Lee IK et al. Diabetic patients suffering dengue are at risk for development of dengue shock syndrome/severe dengue: emphasizing the impacts of co-existing comorbidity(ies) and glycemic control on dengue severity. *J Microbiol Immunol Infect.* 2020;53:69. [PMID: 30146413]

Mamun MA et al. The dengue epidemic in Bangladesh: risk factors and actionable items. *Lancet.* 2019;394:2149. [PMID: 31839186]

Sridhar S et al. Effect of dengue serostatus on dengue vaccine safety and efficacy. *N Engl J Med.* 2018;379:327. [PMID: 29897841]

Wilder-Smith A et al. Misguided approach to dengue vaccine risk. *Science.* 2019;366:1082. [PMID: 31780549]

World Health Organization. Dengue and severe dengue. 2019 Dec 3. <https://www.who.int/en/news-room/fact-sheets/detail/dengue-and-severe-dengue>

World Health Organization. Dengue vaccine: WHO position paper, September 2018—Recommendations. *Vaccine.* 2019;37: 4848. [PMID: 30424888]

4. Hantaviruses



ESSENTIALS OF DIAGNOSIS

- ▶ Transmitted by rodents and cause two clinical syndromes.
- ▶ **Hemorrhagic fever with renal syndrome (HFRS):** mild to severe illness.
- ▶ **Hantavirus pulmonary syndrome (HPS):** 40% mortality rate.

► General Considerations

Hantaviruses are enveloped RNA bunyaviruses naturally hosted in rodents, moles, and shrews. Globally, hantaviruses infect more than 200,000 people annually, and their collective mortality rate is about 35–40%. Hantavirus infection in humans can cause several disease syndromes. HFRS is primarily caused by Dobrava-Belgrade virus, Puumala virus, Seoul virus, and Hantaan virus in Asia and Europe. These viruses are called Old World hantaviruses. Nephropathia epidemica is a milder form of HFRS. Puumala virus is the most prevalent pathogen and is present throughout Europe. The HPS, also known as hantavirus cardiopulmonary syndrome, is caused mainly by Sin Nombre virus and Andes virus, the New World Hantaviruses in Americas. While they share many clinical features, a specific strain is not associated with a specific syndrome and overlap is seen between the syndromes. The primary reservoirs include the field

mouse for Hantaan virus HFRS, the bank vole for Puumala virus, and the deer mouse for SNV-HPS.

Aerosols of virus-contaminated rodent urine and feces are thought to be the main vehicle for transmission to humans. Person-to-person transmission is observed only with the Andes virus. *Occupation is the main risk factor for transmission of all hantaviruses:* animal trappers, forestry workers, laboratory personnel, farmers, and military personnel are at highest risk. Climate change appears to be impacting the incidence of hantavirus infection mainly through effects on reservoir ecology.

► Clinical Findings

A. Symptoms and Signs

Vascular leakage is the hallmark of the disease for both syndromes, with kidneys being the main target with variants associated with HFRS and the lungs with variants associated with HPS.

1. HFRS—HFRS manifests as mild, moderate, or severe illness depending on the causative strain. A 2- to 3-week incubation period is followed by a protracted clinical course, typically consisting of five distinct phases: febrile period, hypotension, oliguria, diuresis, and convalescence phase. Various degrees of kidney involvement are usually seen. Puumala virus infection is often referred to as nephropathia epidemica. Thromboembolic phenomena are also recognized complications. A secondary hemophagocytic lymphohistiocytosis can be seen with HFRS. Pulmonary edema is not typically seen but when present usually occurs in the final stages of disease (oliguric and diuretic phase). Encephalitis and pituitary involvement are rare findings with hantavirus infection, although a few cases are reported with Puumala virus infection. Patients may have persistent hematuria, proteinuria, or hypertension up to 35 months after infection. Smoking appears to exacerbate the viremia with the Puumala virus infection, and bradycardia can also be prominent.

2. HPS—The clinical course of HPS is divided into a febrile prodrome, a cardiopulmonary stage, oliguric and diuretic phase, followed by convalescence. A 14- to 17-day incubation period is followed by a prodromal phase, typically lasting 3–6 days, that is associated with myalgia; malaise; abdominal pain along with nausea, vomiting, and diarrhea; headache; chills; and fever of abrupt onset. An ensuing cardiopulmonary phase is characterized by the acute onset of pulmonary edema. In this stage, cough is generally present, abdominal pain and symptoms as above may dominate the clinical presentation, and in severe cases, significant myocardial depression occurs. Acute kidney injury and myositis may occur. Sequelae include neuropsychological impairments in some HPS survivors.

B. Laboratory Findings

Laboratory features include hemoconcentration and elevation in lactate dehydrogenase, serum lactate, and hepatocellular enzymes. Early thrombocytopenia and leukocytosis (as high as 90,000 cells/mcL [$90.0 \times 10^9/L$] in HPS) are seen in both HFRS and HPS. In HPS, immunoblasts (activated

lymphocytes with plasmacytoid features) can be seen in blood, lungs, kidneys, bone marrow, liver, and spleen.

An indirect fluorescent assay and enzyme immunoassay are available for detection of specific IgM or low-avidity IgG virus-specific antibodies. A quantitative RT-PCR is available; however, the viremia of human hantavirus infections is short-term, and therefore, viral RNA cannot be readily detected in the blood or urine of patients unless for the more readily detected early viremia of the Andes variant.

A plaque reduction neutralization test remains a gold standard serologic assay and distinguishes between the different hantavirus species, although cross reaction between Old and New World viruses exist. This test needs to be performed in a laboratory with appropriate biosafety (level 3).

► Differential Diagnosis

The differential diagnosis of the acute febrile syndrome seen with HFRS or early HPS includes scrub typhus, leptospirosis, and dengue. HPS requires differentiation from other respiratory infections caused by such pathogens as SARS-CoV-2, *Legionella*, *Chlamydia*, and *Mycoplasma*. Coxsackievirus infection should also be considered in the differential diagnosis.

► Treatment

Treatment is mainly supportive. Cardiorespiratory support with vasopressors is frequently needed; extracorporeal membrane oxygenation may be required in severe cases of HPS. Intravenous ribavirin is used in HFRS (Hantaan virus) with some success in decreasing the severity of the kidney injury. Its effectiveness in HPS, however, is not established.

► Prevention

Because infection is thought to occur by inhalation of rodent waste, prevention is aimed at eradication of rodents in houses and avoidance of exposure to rodent excreta, including forest service facilities. Climatic changes often require particular attention to rodent populations in parks. Inactivated vaccines are used in several Asian countries where patients are at risk for HFRS. Vaccines under investigation include a Hantaan/Puumala virus DNA vaccine (delivered via a TriGrid device).

► Prognosis

The outcome is highly variable depending on severity of disease. HPS is a more severe disease than HFRS, with a mortality rate of about 40%. In Sin Nombre virus infections, the persistence of elevated IgG titers correlates with a favorable outcome.

Dheerasekara K et al. Hantavirus infection—treatment and prevention. *Curr Treat Options Infect Dis.* 2020;29:1. [PMID: 33144850]

Munir N et al. Hantavirus diseases pathophysiology, their diagnostic strategies and therapeutic approaches: a review. *Clin Exp Pharmacol Physiol.* 2020. [Epub ahead of print] [PMID: 32894790]

Noh JY et al. Hemorrhagic fever with renal syndrome. *Infect Chemother.* 2019;51:405. [PMID: 31668027]

5. Yellow Fever



ESSENTIALS OF DIAGNOSIS

- ▶ Endemic area exposure: tropical and subtropical South America and Africa.
- ▶ Sudden onset of severe headache, aching in legs, and tachycardia.
- ▶ Brief (1 day) remission, followed by bradycardia, hypotension, jaundice, hemorrhagic tendency.
- ▶ Albuminuria, leukopenia, bilirubinemia.

► General Considerations

Yellow fever is a zoonotic flavivirus infection transmitted by *Aedes* mosquito bites. There are three types of transmission cycles: sylvatic (or jungle; humans working or traveling in the forest are bitten by infected mosquitoes), intermediate (most common type of outbreak in Africa; mosquitoes infect both monkeys and people leading to outbreaks in separate villages), and urban (seen in large epidemics; infected mosquitoes transmit the virus from person to person). Elevated temperatures and increased rainfall are major determinants of transmission.

Yellow fever occurs in 47 endemic countries in Africa and in Central and South America. Around 90% of cases reported every year occur in sub-Saharan Africa. Adults and children are equally susceptible, though attack rates are highest among adult males because of their work habits. Modeling data from Africa in 2013 estimates the annual case load is 84,000 to 170,000 annual cases with 29,000 to 60,000 deaths. The number of people susceptible to infection with yellow fever virus worldwide is estimated to be between 394 million and 473 million.

The last decade has seen a resurgence of yellow fever, likely due to suboptimal vaccination coverage along with waning population-level immunity.

► Clinical Findings

A. Symptoms and Signs

Most persons have no illness or only mild illness. The incubation period is 3–6 days in persons in whom symptoms develop.

1. Mild form—Symptoms are malaise, headache, fever, retroorbital pain, nausea, vomiting, and photophobia. Relative bradycardia (an increase in heart rate of fewer than 10 beats/min for a 1°C increase in temperature), conjunctival injection, and facial flushing may be present.

2. Severe form—Severe illness develops in about 15%. Initial symptoms are similar to the mild form, but brief fever remission lasting hours to a few days is followed by a “period of intoxication” manifested by fever and relative bradycardia (Faget sign), hypotension, jaundice, hemorrhage (gastrointestinal, nasal, oral), and delirium that may progress to coma.

B. Laboratory Findings

Leukopenia, elevated liver enzymes, and bilirubin can occur. Proteinuria is present and usually disappears completely with recovery. Bleeding dyscrasias with elevated prothrombin and partial thromboplastin times, decreased platelet count, and presence of fibrin-split products can also occur.

In the early stages of the disease (up to 10 days), diagnosis is confirmed if yellow fever virus RNA is detected by RT-PCR in blood from a person with no history of recent yellow fever vaccination. PCR determinants can distinguish between wild type virus and vaccine-associated strains.

In later stages, serologic diagnosis can be made by using ELISA to measure IgM 3 days after the onset of symptoms; however, yellow fever vaccine and other flaviviruses, including dengue, West Nile, and Zika viruses, may give a false-positive ELISA test result. Thus, the presence of yellow fever virus-specific IgM antibody and negative ELISA panel for other relevant flaviviruses confirm the diagnosis. If ELISA is positive for other flaviviruses, the more specific plaque reduction neutralization assay should be done in reference laboratories, which measures the titer of the neutralizing antibodies in the serum toward the infecting virus.

► Differential Diagnosis

It may be difficult to distinguish yellow fever from other viral hepatitides, malaria, leptospirosis, louse-borne relapsing fever, dengue, and other hemorrhagic fevers on clinical evidence alone. Albuminuria is a constant feature in yellow fever patients, and its presence helps differentiate yellow fever from other viral hepatitides. Serologic confirmation is often needed.

► Treatment

No specific antiviral therapy is available. Treatment is directed toward symptomatic relief and management of complications. A randomized clinical trial of sofosbuvir for treatment of yellow fever is underway in Brazil.

► Prognosis

The mortality rate of the severe form is 20–50%, with death occurring most commonly between the sixth and the tenth days. Convalescence is prolonged, including 1–2 weeks of asthenia. Infection confers lifelong immunity to those who recover.

► Prevention

The yellow fever vaccine, which is derived from the live attenuated 17D strain (with substrains 17D-204 and 17DD similar in efficacy and side effects) and given as a single dose for a lifetime, is the most effective way to prevent and control disease. A single dose of vaccine in the past was considered to provide lifelong immunity. While the 10-year booster dose is no longer recommended for most people, persistent seropositivity at 8 years post vaccination is only 85% (and below 60% in children vaccinated at 9–12 months of age). Thus, at-risk groups with waning immunity and high probability of exposure may consider receiving a

second dose of vaccine after 10 years (these groups are listed at <https://www.cdc.gov/yellowfever/healthcareproviders/vaccine-info.html>).

Yellow fever vaccine is recommended for persons aged over 9 months who are traveling to or living in areas at risk for yellow fever virus transmission. This vaccine should never be given to children under 6 months old due to their higher risk of developing encephalitis related to the vaccine. *WHO recommends that all endemic countries should include yellow fever vaccine in their national immunization programs.*

The vaccine is contraindicated in persons with severe egg allergies or who are severely immunocompromised, including patients with primary immunodeficiencies, HIV infection with CD4+ count below 200/mcL, thymus disorder with abnormal immune function, malignant neoplasms, transplantation, or immunosuppressive and immunomodulatory therapies. The vaccine should not be given to breastfeeding women or patients over 60 years of age because this age group is at higher risk for viscerotropic and neurologic disease. It should be administered at least 24 hours apart from the measles vaccine. Pregnant women should receive the vaccine only if they cannot defer travel to endemic areas (Chapter 30). Clinicians should be aware of rare but frequently fatal vaccine-induced reactions, including anaphylaxis, yellow fever vaccine-associated viscerotropic disease, and yellow fever vaccine-associated neurologic disease.

A 2017 initiative, the Eliminate Yellow Fever program, is composed of 50 organizations and designed to increase surveillance and control in 40 countries of Africa and the Americas in an attempt to reach a billion at-risk individuals with seroprotection by 2026.

The best personal protective measures are to avoid mosquito bites. If not in an endemic area, the patient should be isolated from mosquitoes to prevent transmission, since blood in the acute phase is potentially infectious.

Campi-Azevedo AC et al. Short-lived immunity after 17DD yellow fever single dose indicates that booster vaccination may be required to guarantee protective immunity in children. *Front Immunol.* 2019;10:2192. [PMID: 31616412]

Figueiredo-Mello C et al. Efficacy of sofosbuvir as treatment for yellow fever: protocol for a randomised controlled trial in Brazil (SOFFA study). *BMJ Open.* 2019;9:e027207. [PMID: 31772079]

World Health Organization. Yellow fever. 2019 Sep 16. <https://www.who.int/csr/disease/yellowfev>

- Complications include microcephaly and ocular abnormalities in infants born to mothers infected during pregnancy, as well as Guillain-Barré.
- There is no effective antiviral or vaccine.

► General Considerations

Zika virus is a flavivirus, akin to the viruses that cause dengue fever, Japanese encephalitis, and West Nile infection.

The virus was noted in Africa and Asia during the 1950s–1980s, but first spread beyond those two continents during 2007 when an outbreak occurred in Yap State, Federated States of Micronesia. A large outbreak occurred in French Polynesia in 2013. The virus then spread to the Western hemisphere and was first noted in northeastern Brazil in 2015, and 239,742 cases were subsequently reported between 2015 and 2018. Zika virus spread rapidly throughout the Americas, including the United States and worldwide (<http://www.who.int/csr/disease/zika/en/>). Despite distinct lineages, Zika virus exists as only one serotype.

Aedes species mosquitoes, particularly *Aedes aegypti*, are primarily responsible for transmission of Zika virus. The biodistribution of the species largely determines the area of prevalence for Zika virus. *Aedes* species mosquitoes are found primarily in the southeastern United States, but one species *Aedes albopictus* may be seen as far north as Pennsylvania and New Jersey. Rarely, a few other mosquito species including *Anopheles* and *Culex* may be competent for the Zika virus. Sexual transmission is reported from males and females to partners via vaginal, anal, or oral sex. Vertical transmission from pregnant woman to fetus is prominent. Transmission via platelet transfusion is also reported.

Since the onset of the first reported cases in the United States in 2015, most cases occur in US territories (largely Puerto Rico). The territorial cases are largely locally acquired and the US state cases are largely travel-acquired. The number of annual cases is diminishing markedly in the United States with a peak in 2016 of 4897 travel-associated cases and 224 locally acquired cases (Florida, 218; Texas, 6). The CDC case count for the year 2020, as of September 3, 2020, reports 1 case (a returning traveler) in the United States and 13 (all locally acquired cases) in the US territories.

► Clinical Findings

A. Symptoms and Signs

The incubation period is 3–14 days. The majority (50–80%) of Zika virus infections are asymptomatic. Symptoms include acute onset fever, maculopapular rash that is usually pruritic, nonpurulent conjunctivitis, and arthralgias, the latter mimicking the symptoms of the chikungunya virus. Rash may outlast the fever but is not always present. Symptoms last up to 7 days. Most infections are asymptomatic. Viral infections most often confused with Zika include dengue and chikungunya virus infections.

OTHER SYSTEMIC VIRAL DISEASES

1. Zika Virus



ESSENTIALS OF DIAGNOSIS

- Most infected persons asymptomatically seroconvert.
- Clinical symptoms are akin to those of chikungunya virus infection but with less arthritis.

B. Laboratory Findings and Diagnostic Studies

The CDC recommends that persons with symptoms of Zika infection be tested if they live in or have traveled recently to an area with active transmission. The CDC no longer recommends testing for asymptomatic pregnant women.

Diagnosis is made by detecting viral RNA (nucleic acid testing) in patients presenting with onset of symptoms less than 7 days. Nucleic acid testing can be performed within 14 days of illness onset. Persons being tested 14 days or more after symptom onset should be tested using IgM serology. The Triplex RT-PCR assay, which detects Zika virus, chikungunya virus, and dengue virus RNA, and the Zika MAC-ELISA, which detects Zika virus IgM antibodies (usually present up to 12 weeks after illness onset), are available. Matched serum and urine specimens should be tested simultaneously. Although not routinely recommended, RT-PCR can be performed on amniotic fluid, CSF, and placental tissue. A positive RT-PCR test definitively makes the diagnosis of Zika virus infection and does not require additional confirmatory testing. A negative test does not exclude the presence of the virus in other tissues and does not rule out infection. Persons with negative nucleic acid tests and symptoms of Zika infection should undergo further testing for Zika virus IgM antibody and other arboviral infections. Serologic testing for Zika virus should only be conducted by laboratories with experience in performing flavivirus serology. Recommended serologic assays include enzyme immunoassays and immunofluorescence assays (which detect IgM antibodies using viral lysate, cell culture supernatant, or recombinant proteins) as well as neutralization assays (such as plaque-reduction neutralization tests). The Zika MAC-ELISA can be performed on serum or CSF. Anti-Zika IgM antibodies are observed in CSF of children with congenital infection. Neutralizing antibodies can cross-react with dengue and other flaviviruses, so samples testing positive should be sent to public health laboratories for confirmation.

In the United States, testing for asymptomatic pregnant women is not currently recommended by the CDC even after travel to an area with Zika activity. The WHO however does still recommend testing via IgM antibody for asymptomatic pregnant women who could have had contact with vector-borne or sexually transmitted Zika virus. In areas with active Zika transmission, asymptomatic pregnant women should be tested for IgM antibody as part of routine obstetric care. Persistent Zika virus RNA in serum has been reported in pregnancy. Pregnant women with confirmed or suspected Zika virus infection may be monitored by serial ultrasounds at 3- to 4-week intervals, assessing fetal anatomy and growth. With a declining prevalence of Zika virus infection, positive antibody tests run the risk of more likely being false-positives and thus the need for the outlined assessments exists.

► Complications

Two neurologic complications are of particular concern: (1) **congenital microcephaly**, often associated with brain calcifications and other abnormalities, first noted during

the outbreak in Brazil; and (2) **Guillain-Barré syndrome**, first noted during the outbreak in French Polynesia. The incidence of Guillain-Barré syndrome is estimated at 2–3 cases per 10,000 Zika virus infections. In addition to microcephaly, Zika causes a spectrum of birth defects of the CNS that collectively are termed "**congenital Zika syndrome**." These include fetal brain disruption sequence, subcortical calcifications, pyramidal and extrapyramidal signs, ocular lesions of chorioretinal atrophy, focal pigmented mottling of the retina, and congenital contractures. Newborns of women infected with Zika virus during pregnancy have a 5–14% risk of congenital Zika syndrome and a 4–6% risk of Zika virus-associated microcephaly. Spontaneous abortions and rare deaths related to Zika virus infection are reported.

As with Ebola virus, the Zika virus can persist in semen for months; in the male reproductive tract the prostate gland and the testes are the presumed reservoirs. Persistence of the virus in the female reproductive tract is possible.

► Treatment

There are no antivirals approved for treatment of Zika virus; thus, management should focus on supportive care. Aspirin and NSAIDs are avoided during illness caused by the flavivirus dengue because of its propensity to cause hemorrhage. Zika virus infections, however, do not appear to be associated with major hemorrhagic complications.

► Prevention

The most effective means is environmental control of mosquitoes and removal of areas where water is stagnant or builds up. Such measures include screens on houses; removal of old tires and debris from endemic areas of infection; and movement toward better living conditions, including air conditioning in impoverished areas. Because of the association between microcephaly and Zika virus infection during pregnancy, pregnant women are advised to avoid travel to areas where Zika virus is circulating (<http://www.who.int/csr/disease/zika/information-for-travelers/en/>). Guidelines for testing of pregnant women potentially exposed are available through the CDC. Infected individuals should refrain from blood donations for several months.

No approved vaccine against Zika virus exists; however several inactivated vaccine candidates have shown the ability to induce neutralizing antibodies based in phase 1 trials. A phase 2 multicenter randomized trial evaluating Zika virus wild type DNA vaccine (NCT03110770) is currently undergoing data analysis. Vaccine candidate evaluation has been hampered by the declining incidence of Zika virus.

Abbink P et al. Zika virus vaccines. *Nat Rev Microbiol*. 2018;16: 594. [PMID: 29921914]

Giron S et al. Vector-borne transmission of Zika virus in Europe, southern France, August 2019. *Eurosurveillance*. 2019;24: 1900655. [PMID: 31718742]

Kovacs A. Zika, the newest TORCH infectious disease in the Americas. *Clin Infect Dis*. 2020;70:2673. [PMID: 31346608]

- Musso D et al. Zika Virus infection—after the pandemic. *N Engl J Med.* 2019;381:1444. [PMID: 31597021]
- Sánchez-Montalvá A et al. Persistence of Zika virus in body fluids—final report. *N Engl J Med.* 2019;380:198. [PMID: 30628425]

2. Chikungunya Fever

Chikungunya (“that which bends up” in the Bantu language Kimakonde) fever is an alphavirus infection transmitted to humans by *A aegypti* and *A albopictus* and is considered a classic “arthritogenic” virus. The virus originated with two strains, one in West Africa and the other in East/Central/Southern Africa. The first documented clinical cases in India were derivative of the E/C/S African strains with later reports of outbreaks in Kenya in 2004. Subsequently, there were reports from areas that adjoin the Indian Ocean, Southeast Asia and its neighboring islands (2005–2007), South India (2005), and the island of La Réunion (2005–2006), with further spread including autochthonous cases in Italy and France (2007). In 2013, the first autochthonous case of chikungunya reported in the western hemisphere occurred on Saint Martin in the Caribbean, with isolates derivative of the East/Central/South Africa strains. Despite these differences, only one serotype exists.

For 2020, the CDC reported 15 travel-associated US cases in eight states (with the largest number of reports from California and New Jersey). Chikungunya virus prevalence is ubiquitous in endemic countries in Africa, the Americas, Asia, and Europe.

Among naïve populations, attack rates are often as high as 50%. On Saint Martin, 39% of infections were asymptomatic. Vertical transmission is documented if the mother is viremic during parturition, and transmission does not appear to occur throughout pregnancy as it does with Zika virus. Infectious virus was isolated from saliva, although transmission from oral secretions is not observed among humans. Endemicity of *A aegypti* in the Americas and the introduction of *A albopictus* into Europe and the New World raise concern for further extension of the epidemic. Case reports show that chikungunya virus may coinfect patients with yellow fever virus, plasmodia, Zika virus, and dengue virus.

► Clinical Findings

A. Symptoms and Signs

After an incubation period of 1–12 days (estimated median 3), there is abrupt onset of fever; headache; intestinal complaints, including diarrhea, vomiting, or abdominal pain; myalgias; and arthralgias/arthritis affecting small, large, and axial joints. The simultaneous involvement of more than 10 joints and the presence of tenosynovitis (especially in the wrist) are characteristic. The *stooped posture* of patients gives the disease its name. Joint symptoms persist for 4 months in 33% and linger for years in about 10%. A centrally distributed pigmented or pruritic maculopapular rash is reported in 10–40% of patients; it can be bullous with sloughing in children. Mucosal disease occurs in about 15%. Facial edema and localized petechiae are

reported. Neurologic complications, including encephalitis, myelopathy, peripheral neuropathy, Guillain-Barré syndrome, myeloneuropathy, and myopathy, are usually found in persons younger than 5 or older than 49 years. Encephalitis occurred in 8.6 per 100,000 persons infected in La Réunion during 2005–2006 with 17% mortality and increased risk of encephalitis among those older than 65 years. Hemorrhagic fever-like presentations are unusual. Coinfection with other respiratory viruses and with dengue is common. Some of the neuropathology may be immune-mediated, and these cases are usually in those over age 20 and associated with longer latencies and better outcomes. Death is rare and usually related to underlying comorbidities. The differential diagnosis includes other tropical febrile diseases, such as malaria, leishmaniasis, or dengue.

B. Laboratory Findings

Diagnosis is made epidemiologically and clinically. Mild leukopenia occurs as does thrombocytopenia, which is seldom severe. Elevated inflammatory markers do not correlate well with the severity of arthritis. Radiographs of affected joints are normal during the acute phase. Bone lesions are visible in some patients with chronic symptoms.

Serologic confirmation requires elevated IgM titers or fourfold increase in convalescent IgG levels using an ELISA. RT-PCR and ELISA are commercially available; no ELISA kit is FDA-cleared. Culture techniques (viral isolation in insect or mammalian cell lines or by inoculation of mosquitoes or mice) require BSL 3 (biosafety level 3) containment. Directions on submitting specimens for testing may be obtained from the CDC Arboviral Diseases Branch, 970-221-6400. Suspected cases in the United States should be promptly reported to public health authorities.

► Complications & Prognosis

Common complications of chikungunya fever are long-term weakness, asthenia, myalgia, arthralgia, and arthritis, noted to be present in 25–66.5% of cases at 1 year. Risk factors for long-term arthralgias include the existence of such symptoms at 4 months after onset of disease and age over 35 years. Persons with preexisting arthritis are also at increased risk for prolonged symptoms after chikungunya infection with polyarthralgias occasionally lasting for years. Nasal skin necrosis is rarely reported. The Guillain-Barré syndrome is also reported. Comorbid conditions, including hypertension, diabetes, and cardiac diseases, may contribute to severe outcomes; although in some series, patients with significant neurologic complications do not show comorbidities. Severe outcomes and higher mortality are reported among more recent Brazilian cases.

► Treatment & Prevention

Treatment is supportive with NSAIDs and corticosteroids. Chloroquine and methotrexate may be useful for managing refractory arthritis. Chronic disease may require disease-modifying antirheumatic drugs, such as the reports from La Réunion where methotrexate was associated with a positive response. No licensed vaccine exists, although at

least 18 vaccines are in trials including inactivated and live attenuated vaccines. A measles-vectored chikungunya virus vaccine (MV-CHIK) is the most advanced vaccine candidate and is in phase 2 clinical trials. Prevention relies on avoidance of mosquito vectors. Transplantation of tissue from immigrants or from travelers to known endemic areas should be discouraged. Prophylaxis with specific chikungunya immunoglobulins may be useful for immunosuppressed persons.

Badawi A et al. Prevalence of chronic comorbidities in Chikungunya: a systematic review and meta-analysis. *Int J Infect Dis.* 2018;67:107. [PMID: 29277382]

Mehta R et al. The neurological complications of chikungunya virus: a systematic review. *Rev Med Virol.* 2018;28:e1978. [PMID: 29671914]

Onuora S. Acute inflammatory arthritis: methotrexate for chronic chikungunya arthritis? *Nat Rev Rheumatol.* 2018;14:122. [PMID: 29416137]

Sales GMPG et al. Treatment of chikungunya chronic arthritis: a systematic review. *Rev Assoc Med Bras (1992).* 2018;64:63. [PMID: 29561944]

Stegmann-Planchard S et al. Chikungunya, a risk factor for Guillain-Barré syndrome. *Clin Infect Dis.* 2020;70:1233. [PMID: 31290540]

50% of cases by recurrent fever and a full recrudescence lasting 2–4 days.

The differential diagnosis includes influenza, Rocky Mountain spotted fever, numerous other viral infections, and, in the right setting, relapsing fevers.

B. Laboratory Findings

Leukopenia with a shift to the left and atypical lymphocytes occurs, reaching a nadir 5–6 days after the onset of illness. Thrombocytopenia may occur. An RT-PCR assay may be used to detect early viremia. Detection of IgM by capture ELISA or plaque reduction neutralization is possible after 2 weeks from symptom onset and is the most frequently used diagnostic tool.

► Complications

Aseptic meningitis (particularly in children), encephalitis, and hemorrhagic fever occur rarely. Malaise may last weeks to months. Fatalities are very uncommon. Rarely, spontaneous abortion or multiple congenital anomalies may complicate Colorado tick fever infection acquired during pregnancy.

► Treatment

No specific treatment is available. Ribavirin has shown efficacy in an animal model. Antipyretics are used, although salicylates should be avoided due to potential bleeding with the thrombocytopenia seen in patients with Colorado tick fever.

► Prognosis

The disease is usually self-limited and benign.

► Prevention

Tick avoidance is the best prevention. The tick season is primarily from March to November, and the ticks mostly live at high altitudes (over 7000 feet) in sagebrush.

McDonald E et al. Notes from the field: investigation of Colorado tick fever virus disease cases—Oregon, 2018. *MMWR Morb Mortal Wkly Rep.* 2019;68:289. [PMID: 30921304]

Rodino KG et al. Tick-borne diseases in the United States. *Clin Chem.* 2020;66:537. [PMID: 32232463]

COMMON VIRAL RESPIRATORY INFECTIONS

1. Severe Acute Respiratory Syndrome—Coronavirus 2019 (SARS-CoV-2)

The COVID-19 pandemic has been both devastating and fast-changing. In an ongoing commitment to offer current and authoritative diagnostic information and treatment recommendations, this section is being updated frequently online in *CMDT Online* (<https://accessmedicine.com/CMDT>). In this printed version of the section, information likely to change over time has been removed and the reader is referred to *CMDTO* for the complete content. The content herein is current as of March 2021. A number of

3. Colorado Tick Fever



ESSENTIALS OF DIAGNOSIS

- ▶ Onset 1–19 days (average, 4 days) following tick bite.
- ▶ Fever, chills, myalgia, headache, prostration.
- ▶ Leukopenia, thrombocytopenia.
- ▶ Second attack of fever after remission lasting 2–3 days.

► General Considerations

Colorado tick fever is a reportable biphasic, febrile illness caused by a reovirus infection transmitted by *Dermacentor andersoni* tick bite. About five cases occur annually, largely among men over age 40. The disease is limited to the western United States and Canada and is most prevalent during the tick season (March to November), typically at 4,000–10,000 feet above sea level in grassy areas. There is a discrete history of tick bite or exposure in 90% of cases. The virus infects the marrow erythrocyte precursors. Blood transfusions can be a vehicle of transmission.

► Clinical Findings

A. Symptoms and Signs

The incubation period is 3–6 days, rarely as long as 19 days. The onset is usually abrupt with a high fever. Severe myalgia, headache, photophobia, anorexia, nausea and vomiting, and generalized weakness are prominent. Physical findings are limited to an occasional faint rash. The acute symptoms resolve within a week. Remission is followed in

authoritative websites provide current statistics about the impact of the pandemic and current guidelines, including <https://www.cdc.gov/coronavirus/2019-ncov/index.html> and <https://coronavirus.jhu.edu/>.

ESSENTIALS OF DIAGNOSIS

- ▶ Wide spectrum of symptoms.
- ▶ Asymptomatic in at least 20–35%.
- ▶ Upper respiratory tract illness with fever and cough most often when symptomatic.
- ▶ The clinical triad of cough, fever, and dyspnea is infrequent (less than 15%).
- ▶ Advanced pulmonary complications (pneumonia, acute respiratory distress syndrome [ARDS]) with fulminant disease.
- ▶ Mortality of 1–21%.
- ▶ High predilection for the elderly, the immunocompromised, those with chronic diseases, those living in crowded conditions.

► General Considerations

In late 2019, a novel coronavirus emerged, spreading quickly from its origin in China across the globe. The CDC-recommended terminology for the virus is SARS-CoV-2, and the illness caused by this virus is called “Coronavirus Disease 2019” or COVID-19.

COVID-19 was declared a pandemic by the WHO on March 11, 2020. The earliest known case in the United States was documented on January 21, 2020, in a man who had recently returned to the state of Washington from China. The first US case that was not associated with travel or contact with infected travellers was identified in February 2020 in Solano, California.

Some COVID-19 strains from Western Europe have enhanced transmissibility as a function of a modified spike protein S. A pattern of mutations is being described as phylogenetic and three main groups comprise current global strains, with ongoing efforts underway to identify new variants as they emerge.

The CDC website provides a complex set of guidelines and suggestions regarding travel (www.cdc.gov). All travelers should be aware of the likelihood of quarantine both abroad and on return based on origin and destination of travel. A case tally and other current information are available through the WHO website (<https://www.who.int/emergencies/diseases/novel-coronavirus-2019>) and, with an interactive map, through The Johns Hopkins University Coronavirus Resource Center website (<https://coronavirus.jhu.edu/map.html>). Highly informative bi-weekly UCSF Medical Grand Rounds focused entirely on COVID-19 since March 19, 2020, to at least March 2021 can be found on YouTube.

Severe COVID-19 disease is hypothesized to occur due to development of an intense and/or prolonged inflammatory reaction, often called a “cytokine storm,” in the later

phase of illness. Specifically, persistent immune activation in predisposed patients can lead to uncontrolled amplification of cytokine production (including interleukin-6 [IL-6]), leading to multiorgan failure and death.

A. Clinical Epidemiology and Transmission

SARS-CoV-2 shows a higher rate of person-to-person spread than the 2003 SARS-CoV-1 virus. R_0 is the basic reproductive number signifying the number of persons infected by an infected individual. Calculations of R_0 for SARS-CoV-2 have varied but the true R_0 likely lies somewhere between 2 and 3. Transmission has been shown to be extremely efficient within higher-density living facilities (such as nursing homes, homeless encampments, jails and prisons, some Native American reservations, and certain employment settings [such as the meat packing plants]). Simply talking (or singing) in close quarters may efficiently spread the virus.

Presymptomatic spread probably accounts for a large number of cases, although the principal mode of transmission is likely respiratory droplets, which can be propelled up to 6 feet by sneezing or coughing (and have been documented to be propelled as far as 27 feet). The degree that SARS-CoV-2 is aerosolized during coughing and respiratory procedures remains unclear, as does whether aerosolized particles contain live virus leading to transmission. The CDC currently recommends that airborne precautions be used in health care settings only for health care providers performing respiratory procedures (such as collecting induced sputum or intubating the patient). While the case-fatality rate was higher with the 2003 SARS-CoV-1, the number of infected cases, a consequence of the disease dynamics, is much higher with SARS-CoV-2 than with either the SARS or MERS viruses. The incubation period for SARS-CoV-2 ranges from about 2 to 24 days with an average of about 5.2 days.

Hospital-related transmission to staff or other patients was reported in 41% of 138 hospitalized patients from Wuhan, China. By mid-April of 2020, over 9400 health care personnel had become infected in the United States and 27 had died. A preliminary study from Birmingham, England, shows that among hospital personnel, the highest rates of disease are encountered among housekeeping staff and physicians on acute medicine (but not emergency medicine) and general medicine services.

Severe disease seems to develop in adults much more often than in children, and symptomatic disease appears to develop in men more often than in women. The coding of the angiotensin-converting enzyme (ACE) receptor protein on the X chromosome and the presence of variants in this protein may explain some of the clinical variation seen.

Children appear to be infected primarily by older family members and less so by school interactions, although these data are preliminary. Children show lower concentrations of ACE-2 receptors in lung tissue, which may explain their lower propensity toward infection. With the advent of COVID-19, the CDC reports a fall in immunization rates for the vaccine preventable diseases of childhood. The unique complications of COVID-19 among children are discussed below.

B. Public Health Concerns

Three factors that are complicating the control of this epidemic virus are (1) its known infectivity of health care workers, (2) its spread by infected individuals during an early asymptomatic phase of illness, and (3) difficulty accessing testing. In the United States, many different versions of nucleic acid testing are offered by the CDC, local and state health departments, commercial testing companies (eg, LabCorp and Quest), and many hospital-associated clinical laboratories.

The use of **personal protective equipment** is mandatory by health care workers in contact with suspect cases and in particular those exposed to secretions, such as anesthesiologists and pulmonologists. The use of cloth face coverings (not necessarily surgical masks) among the general population is recommended by the CDC and is required in many jurisdictions.

Among many COVID-19-related US public health concerns, the most urgent needs include the following: (1) increased availability of masks, personal protection equipment, and ventilators; (2) widespread implementation of containment measures (social distancing and self-quarantining) before the disease spreads exponentially in vulnerable populations; (3) standardization of nucleic acid assays and broadened surveillance to help control infection; and (4) expanded accessibility of serologic tests to determine an individual's exposure history (which will inform the community impact of COVID-19, allow for establishment of contact tracing, determine when social distancing measures can be lifted, and identify recovered patients who can provide convalescent serum); (5) increased attention to minority populations (particularly Black and Latino populations) who are at high risk for infection; (5) standardization of state-by-state data reporting; and (6) vaccine research, including the identification of markers for protection.

Four benchmarks developed by a panel of governmental and academic advisors to recommend the readiness of jurisdictions to ease lockdown restrictions include (1) the ability of hospitals to safely care for patients without requiring a crisis standard of care, (2) the ability of a state to test all who have symptoms, (3) a robust system of contact tracing, and (4) a documented decline in incidence of COVID-19 infection for 14 days.

► Clinical Findings

A. Symptoms and Signs

Many infected individuals are asymptomatic, although the ratio of asymptomatic to symptomatic infection remains unclear and changes as more individuals are tested. People with COVID-19 can manifest a wide range of symptoms from mild to severe illness that begin 2–14 days (the mean is 5 days) after exposure to SARS-CoV-2. The CDC reports that symptomatic patients may have any of the following: cough, fever, chills/rigors, or myalgias. Dyspnea is present in variable numbers and is especially infrequent in children. No one symptom should be used as a discriminant for disease. Less common symptoms include rhinitis;

pharyngitis; abdominal symptoms, including nausea and diarrhea; headaches; anosmia; and ageusia. It appears that 15–20% of people with COVID-19 require hospitalization and 3–5% require critical care.

COVID-19 infection is particularly serious in the elderly and in those with immunocompromising conditions (including post-organ transplant) or chronic diseases (diabetes; hypertension; chronic heart, lung, or kidney disease; and prior stroke). Preliminary evidence suggests that patients with rheumatologic diseases are not at increased risk for coronavirus infection; data describing risk of COVID-19 in people living with HIV are not yet available (see Chapter 31).

While the infection shows a predilection for pulmonary tissues, data regarding susceptibility of persons who smoke cigarettes and those with asthma are unclear.

While pregnant women do not appear to be at increased risk for complications (as they do with influenza infection), the full spectrum of complications associated with pregnancy is not known. Reports of in utero transmission are not confirmed with the duration of IgM to coronavirus in potentially infected neonates much shorter than that seen with other neonatal viral infections. The virus does not appear to be transmitted in breast milk. A team based at the University of California, San Francisco (UCSF) (the PRIORITY study) is assessing prospectively the complications associated with pregnancy, delivery, and breastfeeding. (See <https://www.nejm.org/coronavirus> for review of cases and <https://obgyn.ucsf.edu/block/theme-priority-study> for enrollment of women in the above categories.)

B. Laboratory Findings

Hematologic and blood chemistry findings include neutrophilia, absolute lymphocytosis (using 400 cells/ μL [$0.4 \times 10^9/\text{L}$] as a cutoff), increased absolute lactate dehydrogenase level, and increased liver biochemical tests. Additionally, many reports have accumulated data detailing the initial coagulopathy seen in severe COVID-19, which is identified by elevated D-dimer and fibrin/fibrinogen degradation products; the prothrombin time, partial thromboplastin time, and platelet counts are usually unaffected initially (see Chapter 14). The entity, referred to as **COVID-19-associated coagulopathy**, has laboratory findings that differ from DIC. In COVID-19-associated coagulopathy, fibrinogen levels are higher and platelets levels are more often normal than with DIC.

C. Diagnostic Studies

COVID-19 diagnosis is established using nucleic acid testing. Molecular tests to detect SARS-CoV-2 were first developed in China in January 2020. Since then, many different types of SARS-CoV-2 tests have been developed in thousands of laboratories worldwide. In the United States, the FDA approved the first SARS-CoV-2 PCR test via emergency use authorization (EUA) on February 4, 2020. The first EUA for a SARS-CoV-2 antigen test was issued on May 9, 2020. As of May 13, 2020, the FDA has approved 98 individual SARS-CoV-2 tests under EUAs, including 85 molecular tests, 12 antibody tests, and 1 antigen test.

Importantly, standardization of these tests is far from finalized. The sensitivity of nucleic acid tests from oral swabs is deemed low (35%); nasopharyngeal swabs (63%) or the more invasive bronchoalveolar lavage fluids (91%) are preferred specimens. Sputum is preferred over oropharyngeal specimens, and the virus may be detectable longer in sputum than in other upper respiratory tract samples. Saliva is being evaluated as an easier to obtain and higher yield specimen early in the course of illness; after the first week, endobronchial specimens show better sensitivity. Some tests convert from negative to positive during the course of acute illness. The phenomenon of false positives in low prevalence populations (Bayes theorem) has not received adequate attention with coronavirus, but the caveat that no assay is 100% specific needs to be remembered.

Isolation of the virus by antigen assays more than 10 days after the onset of symptomatic infection (or 15 days after exposure on the average) is usually not associated with replicative, infectious particles.

A variety of laboratories are producing antibody assays to determine immunity and facilitate decision making in return-to-work policies. On April 1, 2020, the first rapid lateral flow assay (Cellest) was approved by the FDA under EUA to detect IgM and IgG antibodies to SARS-CoV-2. Subsequently, several additional tests that can detect SARS-CoV-2 antibodies have received EUAs (<https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations#covid19ivd>). It is not clear whether these assays test for neutralizing antibodies and if neutralizing antibodies are sufficient for control of infection; T cell responses may also be needed. Importantly, the duration that IgM and IgG antibodies to SARS-CoV-2 persist after the infection has been cleared remains unclear, and some patients with mild infection do not mount such antibody responses. Additionally, because most of these assays are not standardized, the results should be interpreted with caution.

A CRISPR-Cas12 lateral flow real-time polymerase chain reaction (RT-PCR) assay using respiratory specimens that is reported to be 100% sensitive and 95% specific is being developed; when marketed, this test will be faster than most currently available PCR tests but the volume of assays that can be carried out is limited.

An unstandardized combination of clinical findings in conjunction with nucleic acid tests are used to make the diagnosis of COVID-19, recognizing that the wide spectrum of clinical findings and the false reassurance of assays are not fully sensitive or specific. Well-standardized serologic assays, when combined with PCR, have the potential to improve sensitivity and accuracy.

D. Imaging

Early in the disease, neither chest radiographs nor chest CT scans provide diagnostic utility, since both may be normal. Later in the disease course, nonspecific diffuse ground-glass opacities and multilobular infiltrates (which often progress to consolidation) may appear (Figure 32–6).

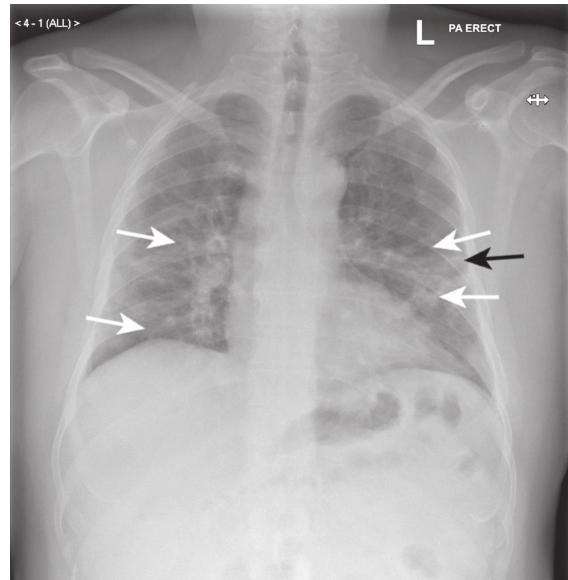


Figure 32–6. Ground-glass opacity. Posterior-anterior chest radiograph of patient A, a man in his 50s with COVID-19 pneumonia. Features include ground-glass opacity in both mid and lower zones of the lungs, which is predominantly peripheral (white arrows) with preservation of lung marking. Linear opacity can be seen in the periphery of the left mid zone (black arrow). (Used, with permission, from Cleverley J, Piper J, Jones MM. The role of chest radiography in confirming COVID-19 pneumonia. BMJ. 2020;370:m2426. © BMJ Publishing Group Ltd.)

Differential Diagnosis

The key element in the differential diagnosis is seasonal influenza infection, which can usually be ruled out by a nasal swab. Concomitant infection with influenza or other respiratory pathogens is possible. Prominent musculoskeletal manifestations, sinusitis, and a sudden onset favor influenza infection, while a more insidious presentation with cough, weakness, malaise, and a gradual worsening of pulmonary symptoms favor SARS-CoV-2 infection.

Complications

Most patients recover without sequelae. In an early Chinese series, 81% of patients were asymptomatic or had mild disease, 14% had severe disease, and 5% were critically ill. In a New York City series, 14% of patients required ICU care, 12% required ventilation, 3% required renal replacement therapy, and 21% died.

One large Chinese study found that the independent predictors of a fatal outcome were age 75 years and older, a history or coronary heart disease, cerebrovascular disease, dyspnea, procalcitonin levels over 0.5 ng/mL, and aspartate aminotransferase levels over 40 units/L.

A clinical risk score calculator to predict critical illness in hospitalized patients with COVID-19 called COVID-GRAM has been validated (<http://118.126.104.170/>);

predictors of clinical deterioration include presence of chest film abnormalities, older age, positive cancer history, increased number of comorbidities, presence of certain signs and symptoms (hemoptysis, dyspnea, and decreased consciousness), and presence of certain laboratory abnormalities (increased neutrophil to lymphocyte ratio, increased lactate dehydrogenase, and increased direct bilirubin).

Some patients progress to ARDS, the care of which requires the involvement of intensivists who can provide guidelines for respiratory support, including appropriate oxygen flow and ventilatory parameters, prone positioning, and hydration status. The US National Institutes of Health (NIH) COVID-19 critical care management guidelines can be found at <https://www.covid19treatmentguidelines.nih.gov/introduction/>.

COVID-19-associated coagulopathy is associated with a particular predisposition to pulmonary emboli and to thrombosis of renal vessels used for continuous renal replacement therapy and, less often, to thrombosis of extracorporeal membrane oxygenation-associated vessels.

Many extrapulmonary complications are reported, and most of these are likely related to SARS-CoV-2-induced inflammatory reactions. A fulminant myocarditis is reported in about 15% of ICU patients, which can be further complicated by heart failure, cardiac arrhythmias, acute coronary syndrome, rapid deterioration, and sudden death. Reported neurologic complications include acute stroke, impaired cognition, and encephalopathy. Neither isolation of the virus from the CNS nor frank meningitis, however, has been reported, while Guillain-Barre syndrome and acute hemorrhagic necrotizing encephalopathy have been reported. Acute musculoskeletal pain is reported in nearly 20%. Hepatic and biliary injury, often acute, and DIC in advanced cases are reported from China. Conjunctivitis is reported from China in about one-third of cases. In the New York, British, and Italian experiences, a hyperinflammatory syndrome akin to an atypical Kawasaki syndrome was noted in children. This has been termed **multisystem inflammatory syndrome in children (MIS-C)** and mimics Kawasaki syndrome in most respects, with reports of more abdominal symptoms with the COVID-19-associated form (see Kawasaki syndrome, below).

The long-term sequelae of COVID-19 are being described; a diversity of syndromes appears to characterize these long-term sequelae and are in the process of further definition. A compilation of nine studies of **post-acute COVID-19 syndrome** from the United States, Europe, and China shows that a male preponderance (52–67%) and an age range veered toward upper middle age (mean, 45–63.2 years; median, 56–70.5 years, not all studies giving both values), with the most common symptoms being fatigue and dyspnea.

The serious psychological sequelae of potentially dying in isolation, of restricted or impaired access to family or friends (especially in nursing homes), and limited funeral services are all relevant issues with which society is grappling. These important aspects require creativity to find tolerable, safe, and sustainable solutions.

► Prevention

Prevention and treatment recommendations are evolving. The usual precautions include handwashing with soap and water for at least 20 seconds, avoiding touching the face, wearing a cloth face covering in public (and, for health care workers, wearing an impermeable mask [eg, N95 mask] if exposure to patients with cough is anticipated), and isolating cases (in particular, removing infected patients from long-term living/care facilities, such as nursing homes, and transportation structures, such as cruise ships).

Social distancing is an important determinant for control of the disease; communities within the United States that practice such distancing show lower R_0 values. Other essential public health priorities should be improving SARS-CoV-2 testing, management, and control in populations with inadequate access to health care (eg, homeless, migrants, and undocumented) as well as in disadvantaged communities across the globe where social distancing is not possible.

The first SARS-CoV-2 vaccine trials began in March 2020. Since then, many candidate vaccines have been launched into preclinical development or authorized for use and involve a variety of technologies (including DNA and RNA platforms, inactivated genes, live-attenuated genes, nonreplicating vectors, protein subunits, and replicating viral vectors). Recent structural biologic studies suggest that antibodies against a prefusion spike protein may facilitate neutralization of the spike protein, the S protein that binds to ACE receptors, and thus a combination of interactive antibodies may be essential for neutralization of COVID-19. Unlike HIV, the rate of mutation of SARS-CoV-2 is relatively low; this is an encouraging aspect in vaccine development and efficacy. The use of simultaneous combination modalities is also encouraged by vaccine developers.

As of April 23, 2021, 13 vaccines have received at least preliminary regulatory authorization and begun to be distributed in one or more countries. In the US, the Pfizer/BioNTech/Fosun Pharma, the Moderna/NIH, and the Johnson & Johnson vaccines are in use, while the AstraZeneca/Oxford University vaccine is also available internationally. Current vaccine recommendations and guidelines from the CDC are available at <https://www.cdc.gov/vaccines/hcp/acip-recommendations/covid-19.html>. The WHO tracks ongoing vaccine trials at <https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines>.

► Treatment

Most infections are mild and require no treatment or only supportive therapy. Because of the biphasic nature of advanced cases, the early course should be managed with antiviral agents, as they become available, and the later cytokine storm phase with anti-inflammatory agents. Please see the most recent update online of this section at CMDTOOnline for current treatment recommendations.

As of March 2021, several agents are being evaluated in clinical trials. Perhaps the most promising is remdesivir (a viral RNA-dependent RNA polymerase [RdRp] inhibitor with known in vitro but limited in vivo activity against the Ebola and Marburg viruses as well as RSV, Lassa virus, and Nipah virus). The preliminary results of the first

remdesivir randomized controlled trials were released on April 29, 2020. One of these, a multicenter trial sponsored by the US National Institute of Allergy and Infectious Diseases (NIAID) called the Adaptive COVID-19 Treatment Trial (ACTT), studied 1063 hospitalized adult patients with advanced COVID-19 and lung involvement and found that those who received remdesivir recovered several days faster than similar patients who received placebo; however, there was no mortality benefit. Additionally, a multicenter Chinese randomized controlled trial of 237 critically ill adult patients showed no clinical benefit in the remdesivir group. Based on these data, remdesivir was approved by the FDA under a EUA on May 1, 2020. It has also been available from the manufacturer (Gilead Sciences) on a compassionate use basis and is being tested in several clinical trials of both critically ill and noncritically ill patients. The rate of adverse events is about 40%, including renal toxicity, diarrhea, transaminitis, and rash, and the drug must be administered intravenously in the hospital, usually in an intensive care unit. Favipiravir is an additional RdRp inhibitor being studied for COVID-19 treatment.

Supportive treatments targeting the SARS-CoV-2-induced immune response, such as IL-6 inhibitors (eg, tocilizumab and sarilumab), are being used based on anecdotal evidence for severe pneumonia. Small early studies have shown some promise, and large clinical trials are underway with the rationale being that high levels of IL-6 are a key component to the cytokine storm associated with advanced coronavirus infection.

Convalescent plasma (ie, plasma from the blood of patients who have recovered from COVID-19) is being used for the critically ill in some centers. While several small series have reported success with the use of convalescent plasma, most available data on its effectiveness are currently anecdotal; clinical trials are ongoing (for US center and patient enrollment, visit www.uscovidplasma.org).

Of the remaining repurposed medications that have been used or studied for treatment of COVID-19, none have shown as much promise as the therapies described above. Hydroxychloroquine was initially prescribed widely for COVID-19. Its mode of action is probably anti-inflammatory, and preliminary studies suggest its role in the management of COVID-19 infection is limited. Its use with azithromycin is potentially dangerous because of the untoward development of cardiac arrhythmias in patients with prolonged QT syndromes, optic neuritis, gastrointestinal intolerance, and anemia. A registry review compared 14,888 coronavirus cases given chloroquine or hydroxychloroquine with or without azithromycin to 81,144 infected controls not taking medication; results showed a decreased in-hospital survival as well as the above noted arrhythmias among patients receiving the medications. The agents should only be used for coronavirus infection as part of a clinical trial.

The anti-HIV combination of lopinavir/ritonavir (Kaletra) was shown to be ineffective by a group of Chinese investigators. The open-label DISCOVERY trial, however, compared adults receiving the triple combination of lopinavir-ritonavir, ribavirin, and interferon beta-1b to adults who received lopinavir-ritonavir alone and found that if given within 7 days of symptom onset, the combination

group showed much faster symptom resolution and shorter duration of hospital stay. Another anti-HIV combination, darunavir/cobicistat, is also under study.

A combination of neutralizing monoclonal antibodies (REGN3048 and REGN3051) is being studied in a first-in-human clinical trial sponsored by the NIAID. Additional agents under investigation include leronlimab (PRO 140; a CCR5 antagonist) and galidesivir (BCX4430; a nucleoside RNA polymerase inhibitor). The Janus kinase (JAK) inhibitor baricitintib is also undergoing clinical trials.

ACE inhibitors and angiotensin receptor blockers do *not* have an impact on disease, and it is recommended that patients who take these medications for other indications continue taking them. No increased risk of COVID-19 exists among patients who take any particular class of antihypertensive agents.

Because pathogenesis includes the action of a serine protease TMPRSS2 with the ACE receptor, two inhibitors of TMPRSS2 are undergoing studies. Camostat mesylate is a TMPRSS2 inhibitor that is available in Japan for other indications (chronic pancreatitis and postoperative reflux esophagitis) and is undergoing study for COVID-19 in Denmark. A related TMPRSS2 inhibitor, nafamostat, is being studied in Germany.

The WHO does not recommend that patients who have or may have COVID-19 restrict the use of ibuprofen if it is needed. Corticosteroids are generally contraindicated for management of coronavirus infections, including for pneumonia, even when their customary use is beneficial, such as for septic shock; the Infectious Diseases Society of America (IDSA) cautions against their use.

The IDSA maintains a freely available website and table outlining the current status of all therapies for coronavirus: <https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/>. In addition, the Pediatric Infectious Diseases Society provides guidance on use of antivirals for children with COVID-19: <https://academic.oup.com/jpids/article/doi/10.1093/jpids/piaa045/5823622>.

The IDSA recommends that all the above therapies, including remdesivir, be administered only as a part of a clinical trial at a facility with the ability to carry out appropriate investigative activities, although given recent data, remdesivir may soon become the standard of care for hospitalized COVID-19 patients.

VTE prophylaxis for COVID-19 patients is indicated and numerous guidelines are being published to assist with full anticoagulation (see Chapter 14). Guidelines published by the American Society of Hematology are available at <https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation>. Higher levels of anticoagulation may be needed in COVID-19 patients, and weight-based anticoagulation is preferred.

► When to Refer

Because most healthy patients are asymptomatic, the exact parameters used for referral are under study. Patients may have atypical manifestations, yet they may be shedding and transmitting the virus. Patients in whom the disease is

suspected should be tested with nasopharyngeal (rather than oral) swabs if symptoms are consistent with COVID-19 infection.

Clinics and hospitals with the resources to screen or test outpatients for COVID-19 should set up a testing area that is isolated from other patient care areas (and outside or in an “open air” environment if possible). These facilities should also designate separate care areas for patients in whom COVID-19 is confirmed or suspected and provide the necessary personal protective equipment for staff who could potentially be exposed to patients infected with SARS-CoV-2. Some cities with sufficient resources are designating coronavirus hospitals.

► When to Admit

The principal complications requiring admission are respiratory. Progression to respiratory failure and ARDS can be rapid, and any patient in a high-risk category for complications (advanced age; immunosuppression; chronic diseases, particularly hypertension, obesity, and diabetes) should be admitted for observation and placed under intensive care based on respiratory parameters.

Andrasfay T et al. Reductions in 2020 US life expectancy due to COVID-19 and the disproportionate impact on the Black and Latino populations. *Proc Natl Acad Sci U S A.* 2021;118:e2014746118. [PMID: 33446511]

Cohen MS. Monoclonal antibodies to disrupt progression of early COVID-19 infection. *N Engl J Med.* 2021;384:289. [PMID: 33471984]

Donnelly JP et al. Readmission and death after initial hospital discharge among patients with COVID-19 in a large multihospital system. *JAMA.* 2020;e2021465. [PMID: 33315057]

Gandhi RT et al. Mild or moderate Covid-19. *N Engl J Med.* 2020;383:1757. [PMID: 32329974]

Heaton PM. The COVID-19 vaccine – development multiverse. *N Engl J Med.* 2020;383:1986. [PMID: 32663910]

Huang C et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet.* 2021;S0140-6736(20)32656-8. [PMID: 33428867]

Islam N et al. Physical distancing interventions and incidence of coronavirus disease 2019: natural experiment in 149 countries. *BMJ.* 2020;370:m2743. [PMID: 32669358]

2. Respiratory Syncytial Virus (RSV) & Other Paramyxoviruses



ESSENTIALS OF DIAGNOSIS

- ▶ RSV is a major cause of morbidity and mortality at the extremes of age (< 5 years and > 65 years).
- ▶ Treatment is largely supportive.
- ▶ No active vaccination for RSV is currently available.

► General Considerations

Respiratory syncytial virus (RSV) is a paramyxovirus that causes annual outbreaks during the wintertime with usual onset of pulmonary symptoms between mid-October and

early January in the continental United States. Outside the United States, RSV usually peaks during wet months in areas with high annual precipitation and during cooler months in hot and dry areas. Infections occur earlier in urban areas.

There are two major subtypes, A and B, and it appears that the A subtype is associated with disease severity. RSV is the leading cause of hospitalization in US children, with annual hospitalization rates of 6 per 1000 children younger than 5 years. Prematurity and bronchopulmonary dysplasia are major risk factors for severe disease. Early RSV bronchiolitis in children, along with a family history of asthma, are associated with persistence of airway reactivity later in life.

RSV also causes upper and lower respiratory tract infection in adults, with the virus entering through contact with mucous membranes. RSV occurs with increasing severity in those with comorbid conditions, older adults (accounting for a rate of 4 per 1000 hospitalizations and 14,000 deaths annually), persons with severe combined immunodeficiency, and patients after lung or bone marrow transplantation (because CD8 T cells are not available for viral clearance). An interleukin-1 receptor polymorphism is associated with more severe bronchiolitis. Recurrences occur throughout life. The average incubation period is 5 days. Up to 10% of disease classified as invasive pneumococcal disease is thought to be RSV or influenza.

In immunocompromised patients, such as bone marrow transplant recipients, serious pneumonia can occur, and outbreaks with a high mortality rate (over 70%) are reported.

Other paramyxoviruses important in human disease include human metapneumovirus, parainfluenza virus, and Nipah virus.

Human metapneumovirus is a ubiquitous seasonal virus circulating during late winter to early spring. It is divided into subgroups A and B. Metapneumovirus accounted for 7.3% of childhood (younger than 16 years old) pneumonia in a Norwegian series of 3650 patients in which RSV accounted for 28.7%. Clinical presentations range from mild upper respiratory tract infections to severe lower respiratory tract infections (eg, bronchiolitis, croup, and pneumonia). Lower respiratory tract (sometimes severe) infections are observed among immunocompromised and elderly adults, especially residents of nursing homes. In lung transplant recipients, human metapneumovirus is a common cause of respiratory illness and may increase the risk of acute and chronic graft rejection. Ribavirin appears to be well tolerated in lung transplant recipients with metapneumovirus infection. The control of RSV infection in modeling studies reduces the incidence of human metapneumovirus infection.

Human parainfluenza viruses (HPIVs) are commonly seen in children and are the most common cause of laryngotracheitis (croup). Four different serotypes are described, and they differ in their clinical presentations as well as epidemiology. HPIV-1 and HPIV-2 are responsible for croup. HPIV-3 is associated with bronchiolitis and pneumonia. HPIV-4 is a less frequently reported pathogen. Reinfections are common throughout life. HPIVs can also

cause severe disease in older individuals, immunocompromised persons, and patients with chronic illnesses.

Nipah virus is a highly virulent paramyxovirus first described in 1999. Cases are concentrated mainly in Southeast Asia (Malaysia, Singapore, Bangladesh, and India). Fruit bats are identified as the natural host of the virus. An outbreak of 14 cases, 8 fatal, occurred in Bangladesh associated with drinking date palm sap between 2010 and 2014. Direct pig-human, cow-human, human-human, and nosocomial transmission are reported. Nipah virus causes acute encephalitis with a high fatality rate (67–92%), although respiratory symptoms are also described. Cranial nerve palsies, encephalopathy, and dystonia are among neurologic sequelae (15–32%) seen in infected individuals. Relapses occurring weeks and months after initial infection are described (3.4–7.5%).

► Clinical Findings

A. Symptoms and Signs

In RSV bronchiolitis, proliferation and necrosis of bronchiolar epithelium develop, producing obstruction from sloughed epithelium and increased mucus secretion. Signs of infection include low-grade fever, tachypnea, and wheezes. Apnea is a common presenting symptom. Hyperinflated lungs, decreased gas exchange, and increased work of breathing are present. Pulmonary hemorrhage is reported. *In children, RSV is globally the most common cause of acute lower respiratory infection and a common cause of acute and recurrent otitis media.*

B. Laboratory Findings

A rapid diagnosis of RSV infection is made by viral antigen identification of nasal washings using an ELISA or immunofluorescent assay; PCR-based rapid tests are also used. Multiplex assays in conjunction with influenza A and B tests are available commercially. RSV viral load assay values at day 3 of infection may correlate with requirement of intensive care and respiratory failure in children.

Human metapneumovirus is best diagnosed by PCR. Tests for rapid detection of viral antigens with immunofluorescence, ELISA, and PCR techniques are widely available for detection of HPIV. Culture may also be used. ELISA (serum and CSF) and PCR (urine and respiratory secretions but not blood) are both used for Nipah virus infection diagnosis.

► Treatment & Prevention

Treatment of RSV consists of supportive care, including hydration, humidification of inspired air, antibiotic therapy (to reduce other respiratory morbidity) if concomitant bacterial pneumonia is suspected, and ventilatory support as needed. Neither bronchodilating agents nor corticosteroids show efficacy in bronchiolitis although individual patients with significant bronchospasm or history of asthma may respond to them.

The use of aerosolized ribavirin or RSV-enriched IVIG, or both, can be considered in high-risk patients, such as those

with a history of bone marrow transplantation, and appears to lessen mortality. Azithromycin therapy during RSV infection has been shown to reduce the probability of recurrent wheezing during the subsequent year by approximately 50%.

Several additional agents are under study for treatment of RSV. They include a small molecule RSV-F inhibitors (such as JNJ-53718678 [NCT02387606 and NCT03379675], presatovir [NCT02135614], BTA-C585 [NCT02718937], ziresovir [NCT02654171 and NCT02460016], and MDT-637 [NCT01355016]) and antibody-like RSV-F inhibitors (such as ALX-0171 [NCT02979431 and NCT03418571]).

The prophylactic monoclonal antibody palivizumab, while recommended for and effective in high-risk infants (premature infants less than 32 weeks gestational age as well as infants 32- to 25-week gestational age with additional risk factors such as congenital heart and lung diseases and Down syndrome), is not of proven efficacy among adults with RSV. The monoclonal antibody nirsevimab is also effective in preventing RSV-associated lower respiratory tract infections in premature infants.

No RSV vaccine is currently commercially available; however, there are many undergoing clinical trials in a variety of target populations, including neonates, children, pregnant women, and older adults.

Prevention in hospitals entails rapid diagnosis, hand washing contact isolation, and perhaps passive immunization. (Passive immunization is costly but is associated with improved antiviral titers in hematologic stem cell transplant recipients.) The use of conjugated pneumococcal vaccination appears to decrease the incidence of concomitant pneumonia associated with viral infections in children in some countries. Viral shedding averages 11 days and correlates inversely with age and directly with severity of infection.

Therapeutic modalities for human metapneumovirus and parainfluenza virus infections under investigation include intravenous ribavirin administration.

Elawar F et al. Pharmacological targets and emerging treatments for respiratory syncytial virus bronchiolitis. *Pharmacol Ther.* 2021;220:107712. [PMID: 33121940]

Griffin MP et al; Nirsevimab Study Group. Single-dose nirsevimab for prevention of RSV in preterm infants. *N Engl J Med.* 2020;383:415. [PMID: 32726528]

Madhi SA et al. Respiratory syncytial virus vaccination during pregnancy and effects in infants. *N Engl J Med.* 2020;383:426. [PMID: 32726529]

3. Seasonal Influenza

-  **ESSENTIALS OF DIAGNOSIS**
- Cases usually in epidemic pattern.
 - Onset with fever, chills, malaise, cough, coryza, and myalgias.
 - Aching, fever, and prostration out of proportion to catarrhal symptoms.
 - Leukopenia.

► General Considerations

Influenza (an orthomyxovirus) is a highly contagious disease transmitted by the respiratory route in humans. Transmission occurs primarily by droplet nuclei rather than fomites or direct contact. There are three types of influenza viruses that infect humans. While type A can infect a variety of mammals (humans, swine, horses, etc) and birds, types B and C almost exclusively infect humans. Type A viruses are further divided into subtypes based on the hemagglutinin (H) and the neuraminidase (N) expressed on their surface. There are 18 subtypes of hemagglutinin and 11 subtypes of neuraminidase.

Annual epidemics usually appear in the fall or winter in temperate climates. Up to 5 million cases of severe influenza are estimated by the WHO to occur annually, with up to 0.5 million annual deaths. Influenza epidemics affect 10–20% of the global population on average each year and are typically the result of minor antigenic variations of the virus, or **antigenic drift**, which occur often in influenza A virus. On the other hand, pandemics—associated with higher mortality—appear at longer and varying intervals (decades) as a consequence of major genetic reassortment of the virus (**antigenic shift**) or adaptation of an avian or swine virus to humans (as with the pandemic H1N1 virus of 1918) (https://www.who.int/influenza/surveillance_monitoring/updates/latest_update_GIP_surveillance/en).

The highly pathogenic avian influenza subtypes are discussed in the next section. The novel swine-origin influenza A (pandemic H1N1) virus emerged in Mexico in 2009 and quickly spread throughout North America and the world causing a pandemic. This virus originated from triple-reassortment of North American swine, human, and avian virus lineages and Eurasian swine virus lineages and replaced the previous H1N1 seasonal virus.

► Clinical Findings

A. Symptoms and Signs

Type A and B seasonal influenza viruses produce clinically indistinguishable infections, whereas type C usually causes mild illness. The incubation period is 1–4 days. In unvaccinated persons, uncomplicated influenza often begins abruptly. Symptoms range widely from nearly asymptomatic to a constellation of systemic symptoms (including fever, chills, headache, malaise, and myalgias) and respiratory symptoms (including rhinorrhea, congestion, pharyngitis, hoarseness, nonproductive cough, and substernal soreness). Gastrointestinal symptoms and signs may occur, particularly among young children with influenza B virus infections. Fever lasts 1–7 days (usually 3–5). Elderly patients especially may present with lassitude and confusion, often without fever or respiratory symptoms. Signs include mild pharyngeal injection, flushed face, and conjunctival redness. Moderate enlargement of the cervical lymph nodes and tracheal tenderness may be observed. The presence of fever (higher than 38.2°C) and cough during influenza season is highly predictive of influenza infection in those older than 4 years.

B. Laboratory Findings

Rapid influenza diagnostic tests for detection of influenza antigens from nasal or throat swabs are widely available, highly specific, and produce fast results but have low sensitivity leading to high false-negative results. Because of this, the CDC recommends empirically treating patients in whom influenza is suspected. Testing is not necessary unless the patient is ill enough to require admission to the hospital. Not all commercial rapid influenza diagnostic tests can differentiate between influenza A and influenza B, and none of the available rapid influenza diagnostic tests can provide information on influenza A subtypes. Newer digital immunoassays and rapid nucleic acid amplification tests are more sensitive than traditional rapid influenza diagnostic tests; however, the sensitivity of newer PCR techniques is compromised early in the season during low prevalence periods. A nasopharyngeal swab, nasal aspirate, combined nasopharyngeal swab with oropharyngeal swab, or material from a bronchoalveolar lavage can be tested for any influenza strain. When influenza pneumonia is suspected, lower respiratory tract specimens should be collected and tested for influenza viruses by RT-PCR or the above assays.

► Differential Diagnosis

The differential diagnoses for influenza-like infections include a variety of viral respiratory infections (SARS-CoV-2, parainfluenza, RSV, atypical dengue, adenovirus, enterovirus, coronavirus) or other viral infections (flavivirus, CMV, EBV, acute HIV infection), as well as bacterial infections such as mycobacterial infection (atypical pneumonia), pertussis, and Legionnaire disease. Epidemiologic factors can suggest Legionnaire (elderly smokers). Chronicity of cough may suggest adenovirus, mycobacterial, or pertussis infection. Leukocytosis and lymphadenopathy are more often seen with CMV and EBV. Distinguishing influenza from dengue requires attention to rhinitis (influenza) and thrombocytopenia (dengue).

► Complications

Hospitalization or ICU admission for influenza is often a consequence of diffuse viral pneumonitis with severe hypoxemia and sometimes shock. Patients with asthma, residents of nursing homes and long-term care facilities, adults aged 65 years or older, persons who are morbidly obese, and persons with underlying medical conditions (pulmonary, renal, cardiovascular, hepatic, hematologic, neurologic, and neurodevelopmental conditions; and immune-deficient conditions, such as HIV, diabetes, and cirrhosis) are at high risk for complications. Infection during pregnancy increases the risk for hospitalization and may be associated with severe illness, sepsis, pneumothorax and respiratory failure, spontaneous abortion, preterm labor, and fetal distress.

Influenza causes necrosis of the respiratory epithelium, increased adherence of bacteria to infected cells, and ciliary dysfunction, which predispose to secondary bacterial infections. Pneumococcal pneumonia is the most common

secondary infection, and staphylococcal pneumonia is the most serious. *Haemophilus* spp infections also occur. Other frequent complications are acute sinusitis, otitis media, and purulent bronchitis.

Cardiovascular diseases are a complication of influenza infection, in particular among older adults, and influenza is postulated to be a significant trigger for myocardial infarction, cerebrovascular disease, and sudden death. Several studies suggest that influenza vaccination has protective effect against major adverse cardiovascular events. Neurologic complications, including seizures and encephalopathy, may occur. Encephalopathic complications of influenza are uncommon.

Reye syndrome is a rare and severe complication of influenza (usually B type) and other viral diseases (especially varicella), particularly in young children. It consists of rapidly progressive hepatic failure and encephalopathy, and there is a 30% mortality rate. The pathogenesis is unknown, but the syndrome is associated with aspirin use in the management of viral infections.

Treatment

Treatment is supportive. Antiviral therapy should be considered for all persons with acute illness, in particular those at high risk for developing complications who have a suggestive clinical presentation or with laboratory-confirmed influenza. Clinical trials show a reduction in the duration of symptoms, hospital admissions, as well as secondary complications, such as otitis, sinusitis, or pneumonia, but not mortality when using these agents. Maximum benefit is expected with the earliest initiation of therapy. Although the benefit of antiviral therapy after 48 hours of illness is reduced, it should be initiated if the patient is hospitalized or critically ill. Benefit has been noted up to 4–5 days into illness.

The antiviral treatment of choice should be based on the susceptibility of the circulating virus. Since high levels of resistance to the adamantanes (amantadine and rimantadine) persist among seasonal H1N1 and H3N2 influenza A viruses and these agents are not effective against influenza B viruses, amantadine and rimantadine are not recommended for treatment.

Three neuraminidase inhibitors are FDA approved for treatment of influenza A and B: oral oseltamivir, inhaled zanamivir, and intravenous peramivir. The CDC recommends treatment with **oral oseltamivir** (75 mg twice daily for 5 days) as the drug of choice for patients of any age, pregnant women, and patients who are hospitalized or have complicated infection. Absorption of oral oseltamivir is considered reliable, except in patients with impaired gastric motility or gastrointestinal bleeding.

Inhaled zanamivir (10 mg, 2 inhalations twice daily for 5 days) is indicated for uncomplicated acute influenza in patients 7 years and older, is relatively contraindicated among persons with asthma because of the risk of bronchospasm, and is not formulated for use in mechanically ventilated patients. Inhaled zanamivir lacks efficacy in pneumonia, probably due to poor bioavailability in the peripheral lungs.

Intravenous peramivir (600 mg in single dose) is used for outpatient treatment of uncomplicated infection in

patients 18 years and older and is recommended when there is a concern about inadequate oral absorption of oseltamivir. The efficacy of peramivir in patients with severe illness and in patients with influenza B is not well established. Some studies demonstrated that repeated doses for up to 5 days of intravenous peramivir is safe, effective and shorten the duration of influenza illness.

Resistance to neuraminidase inhibitors (oseltamivir, zanamivir, and peramivir) can occur during or after prolonged use in immunocompromised patients, particularly in persons who have undergone hematopoietic stem cell transplant. Intravenous zanamivir is an investigational drug that could be requested for clinical use if there is a concern for oseltamivir-resistant influenza strain. Laninamivir is a long-acting inhaled neuraminidase inhibitor used for the treatment of seasonal influenza, including infection caused by oseltamivir-resistant virus. It is licensed in Japan and South Korea but not in the United States.

Baloxavir (a selective inhibitor of influenza cap-dependent endonuclease that is given as a single oral dose) is FDA-approved for treatment of uncomplicated influenza A and B infections. It is given as 40 mg or 80 mg orally once daily depending on weight (the higher dose for persons 80 kg or more) and should be given within the first 48 hours of infection. Its side effects include diarrhea and bronchitis, and to date, its effects in patients older than 65 years or younger than 12 years are not established. Baloxavir's unique mechanism of action will likely make it useful as part of multidrug therapy for resistant disease. For complicated disease, especially in immunosuppressed patients, the combination of oseltamivir, amantadine, and ribavirin appears to produce faster viral clearance but no definite clinical improvement.

The first class of organosilanes have potent antiviral activity against influenza A viruses that are resistant to amantadine and oseltamivir. Dapivirine, an FDA-approved HIV nonnucleoside reverse transcriptase inhibitor, has broad-spectrum antiviral against multiple strains of influenza A and B viruses. Iminosugars are also under study. Updated advice is available at <http://www.cdc.gov/flu/index.htm>.

Prognosis

The duration of the uncomplicated illness is 1–7 days, and the prognosis is excellent in healthy adults and children. Hospitalization typically occurs in those with underlying medical disease, at the extremes of age, and in pregnant women. *Most fatalities are due to bacterial pneumonia, although exacerbations of other disease processes, in particular cardiac diseases, occur.* Pneumonia resulting from influenza has a high mortality rate among pregnant women and persons with a history of rheumatic heart disease. Mortality among adults hospitalized with influenza ranges from 4% to 8%, although higher mortality (greater than 10–15%) may be seen during pandemics and among immunocompromised individuals. At least 64% of pneumonia and influenza deaths occurred among elderly persons in the United States, who comprised only 15% of the population.

If the fever recurs or persists for more than 4 days with productive cough and white cell count over 10,000/mcL ($10.0 \times 10^9/L$), secondary bacterial infection should be suspected.

► Prevention

Annual administration of influenza vaccine is the most effective measure for preventing influenza and its complications. Seasonal influenza vaccines can reduce influenza hospitalizations by an estimated 61%. Vaccination of health care workers is associated with decreased mortality among hospitalized patients and those in long-term care facilities. Vaccination prevents influenza illness among pregnant women and their infants during the first months of life.

The ACIP and the American College of Obstetricians and Gynecologists' Committee recommend annual influenza vaccination for all persons over 6 months of age with no contraindications. Vaccination is emphasized for high-risk groups and their contacts and caregivers.

Several Cochrane database analyses have examined the efficacy of the influenza vaccines in select populations. The studied groups include patients with COPD (a documented reduction in exacerbations with inactivated vaccine), the elderly (where vaccination shows some efficacy), adults with cancer (weak evidence, some lower mortality and influenza-related outcomes), healthy adults (established efficacy with inactivated vaccine, but only modest effects in pregnant women and newborns), and healthy children (where both live and inactivated vaccines lower the rate of influenza infections).

Other reviews establish the efficacy and safety of influenza vaccination in patients with rheumatoid arthritis, asthma, or myasthenia gravis, and elderly nursing home patients. The obese have an impaired response to the influenza vaccine.

Multiple influenza vaccine products are licensed in the United States and available from different manufacturers (see Table 30–8). These include inactivated influenza vaccines (standard- or high-dose, trivalent [IIV3] or quadrivalent [IIV4], adjuvanted or unadjuvanted), recombinant vaccines (trivalent [RIV3] or quadrivalent [RIV4]), and live attenuated influenza vaccine (LAIV4). All trivalent vaccines contain antigens from one strain each of influenza A (H1N1), influenza A (H3N2), and influenza B. Quadrivalent vaccines include an additional influenza B strain. The CDC does not endorse one influenza vaccine product over another, although each influenza vaccine product has different age indications and contraindications. The CDC publishes its annual influenza recommendations in the late summer (www.cdc.gov/mmwr).

LAIV4 (which was not recommended by the CDC during the 2016–2017 and 2017–2018 seasons in the Northern Hemisphere due to concerns about its effectiveness against influenza viruses in prior years) is considered an acceptable option for groups in whom it is indicated.

Adults over the age of 18 years, including pregnant women, can receive any influenza vaccine, with few exceptions. Patients 65 years or older should receive a high-dose trivalent inactivated influenza vaccine containing four times more hemagglutinin than standard dose (Fluzone

High Dose), or Fluad, a trivalent inactivated influenza vaccine that contains an adjuvant (MF59), which enhances the immune response to the vaccine. Adults older than 65 years can use any IIV or RIV intramuscular vaccine; in a large randomized trial, high-dose IIV3 showed superior efficacy over standard-dose IIV3 and may provide better protection. Some data suggest intradermal vaccination is more effective than intramuscular vaccination in the elderly. The herpes zoster vaccine can be safely coadministered with the seasonal influenza vaccines in patients over 50 years of age, with similar immunogenicity.

For patients with cancer, chemotherapeutic regimens containing rituximab show persistent perturbations of B-cell and Ig synthesis, and these modifications decrease humoral responses to the influenza vaccine. Adjuvanted vaccine is efficacious but has resulted in brief disease exacerbation in persons with psoriatic arthritis taking TNF-alpha inhibitors.

Vaccination is contraindicated for persons with a history of severe allergic reaction to an influenza vaccine. Precautions should be taken if patients report a history of Guillain-Barré syndrome 6 weeks following an influenza vaccine and if patients have a moderate to severe acute illness with or without fever until clinical improvement. Persons with a history of egg allergy with hives only may receive any recommended influenza vaccine. Those with more severe allergic reactions to eggs may receive any recommended vaccine under close observation in a health care facility under the supervision of a provider with experience treating severe allergic reactions. Only the recombinant vaccine and the US cell culture-based inactivated (Flucelvax Quadrivalent, ccIIV4) vaccine are egg-free. Additional vaccine information can be found at <http://www.cdc.gov/flu/professionals/vaccination/index.htm>.

When antiviral chemoprophylaxis is used, it prevents 70–90% of influenza infections. *Chemoprophylaxis is not routinely recommended and is not recommended prior to exposure to prevent development of resistance.* Chemoprophylaxis may be considered for persons at increased risk for complications from infection who are exposed to an infected patient within 2 weeks of vaccination, for persons unlikely to respond to vaccination because of immunosuppression after exposure to an infected person, for persons for whom vaccination is contraindicated and who are at high risk for complications after exposure to an infected person, and for prevention of infection in residents of institutions during an outbreak. Alternatively, a person can be monitored closely, and antiviral therapy initiated at the first onset of symptoms after exposure. Initiation of chemoprophylaxis is not recommended more than 48 hours after exposure. Patients taking chemoprophylaxis should seek urgent medical care if an influenza-like illness develops.

Chemoprophylaxis against influenza A and B is accomplished with daily administration of the neuraminidase inhibitors oseltamivir (75 mg/day, oral) or zanamivir (10 mg/day, inhaled) to continue through 7 days after last known exposure. For outbreak control in long-term care facilities and hospitals, a minimum of 2 weeks is recommended, including in vaccinated persons if the seasonal

vaccine is not well matched to the circulating strain, to continue until 1 week after identification of the last known case. Zanamivir should not be given as chemoprophylaxis to asthmatic persons, nursing home residents, or children younger than 5 years.

Breakthrough infections with influenza occur with neuraminidase inhibitors (in a study with zanamivir) and with vaccination. The efficacy of chemoprophylaxis is proven for individuals and households but not community settings.

Hand hygiene and surgical facemasks appear to prevent household transmission of influenza virus isolates when implemented within 36 hours of recognition of symptoms in an index patient. Such nonpharmaceutical interventions assist in mitigating the spread of pandemic and interpan-demic influenza to nonvaccinated persons. In one study, patients with seasonal H1N1 influenza infection were infectious from 1 day before to about 7 days following illness onset. Children and immunosuppressed persons exhibit prolonged viral shedding and may be infectious longer. Winter school breaks during periods of high influenza transmission appear to decrease rates of visits to primary care practitioners for influenza illness among children and adults.

Any hospital patient in whom the infection is suspected should be isolated in an individual room with standard and droplet precautions. CDC guidelines recommend the equivalent of N95 masks for aerosol-generating procedures (eg, bronchoscopy, elective intubation, suctioning, administering nebulized medications). For such procedures, an airborne infection isolation room can be used, with air exhausted directly outside or recirculated after filtration by a high efficiency particulate air (HEPA) filter. Strict adherence to hand hygiene with soap and water or an alcohol-based hand sanitizer and immediate removal of gloves and other equipment after contact with respiratory secretions is essential. Pre-cautions should be maintained until 7 days from symptom onset or until 24 hours after symptom resolution, whichever is longer. Postexposure prophylaxis or close monitoring and early treatment should be considered for close contacts of patients who are at high risk for complications of influenza and may be considered for health care personnel, public health workers, or first responders who experienced a recognized, unprotected close contact exposure to a person with influenza virus infection during that person's infectious period.

A regimen of dose sparing vaccination (to 3.5 mcg) is advocated by some providers to address the extreme shortage of influenza vaccine, particularly in developing world countries, with adequate vaccination against all components except H3N2, where there is reduced seroconversion.

► When to Admit

- Limited availability of supporting services.
- Pneumonia or decreased oxygen saturation.
- Changes in mental status.
- Consider with pregnancy.

Centers for Disease Control and Prevention (CDC). FluView: a weekly U.S. influenza surveillance report. <https://www.cdc.gov/flu/weekly>

Cochrane Library. Influenza: evidence from Cochrane Reviews. <https://www.cochranelibrary.com/collections/doi/10.1002/14651858.SC000006/full>

Cohen C et al. Vaccinating mothers to protect their babies against influenza. *J Infect Dis.* 2020;221:5. [PMID: 31671176]

Ferdinands JM et al. Waning of influenza vaccine protection: exploring the trade-offs of changes in vaccination timing among older adults. *Clin Infect Dis.* 2020;70:1550. [PMID: 31257422]

Grohskopf LA et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices—United States, 2020–21 influenza season. *MMWR Recomm Rep.* 2020;69:1. [PMID: 32820746]

Whitley RJ et al. Resistance of influenza virus to antiviral medications. *Clin Infect Dis.* 2020;71:1092. [PMID: 31538179]

4. Avian Influenza

ESSENTIALS OF DIAGNOSIS

- ▶ Most human cases occur after exposure to infected poultry.
- ▶ Clinically indistinguishable from seasonal influenza.
- ▶ Epidemiologic factors assist in diagnosis.
- ▶ Rapid antigen assays confirm diagnosis but do not distinguish avian from seasonal influenza.

► General Considerations

Zoonotic influenza viruses are distinct from human seasonal influenza viruses and do not easily transmit between humans. In addition, a number of viral genetic changes are required for adaptation to humans. For avian influenza viruses, birds are the natural hosts. Around the world and in North America, avian influenza A outbreaks occur in poultry from time to time (including a 2016 outbreak in Dubois County, Indiana, with avian but no human cases), and the virus has become endemic in poultry in some countries, mostly in Southeast Asia and Egypt. Occasionally, avian influenza viruses may infect humans or other mammals, including domestic cats and dogs. Illness in humans ranges from mild disease to rapid progressive severe disease and death depending on the subtype.

The primary risk factor for human infection is direct or indirect exposure to infected live or dead poultry or contaminated environments, such as live bird markets. Slaughtering and handling carcasses of infected poultry are also risk factors.

The emergence of H5, H7, and H9 avian influenza virus subtypes in humans raises concern that the virus may undergo genetic reassortment or mutations in some of the genes and develop greater human-to-human transmissibility with the potential to produce a global pandemic. All fatal avian influenza virus infections acquire their internal

gene segments from H9N2 viruses, the most widespread avian influenza subtype.

Human infections with H5N1 viruses have been reported to WHO from 16 countries, the first report in the Americas was in Canada in 2014, and approximately 60% of the cases have died. Infection with H7N9 avian influenza virus was first reported in China in 2013. Since then, many cases have been reported around the world with an average case fatality rate of 40%. Infections with other H7 avian influenza viruses (H7N2, H7N3, and H7N7) have occurred sporadically around the world. Rare human cases of influenza H9N2 are also reported.

► Clinical Findings

A. Symptoms and Signs

Distinguishing avian influenza from regular influenza is difficult. History of exposure to dead or ill birds or live poultry markets in the prior 10 days, recent travel to Southeast Asia or Egypt, or contact with known cases should be investigated. Patients infected by H5N1 or H7N9 avian influenza A viruses have an aggressive clinical course. The symptoms and signs include fever followed by lower respiratory symptoms (cough, dyspnea). Upper respiratory tract symptoms are less common. Gastrointestinal symptoms are reported more frequently in H5N1 infections. Conjunctivitis is reported in influenza H7 infections. Other systems can also be involved leading to neurologic manifestations (encephalopathy, seizure) and liver impairment. Prolonged febrile states and generalized malaise are common. Respiratory failure, multiorgan dysfunction, and septic shock are the usual cause of death. Bacterial superinfections are reported.

For human infections with H7N7 and N9B2 avian influenza virus infections, most cases have been mild with a few cases hospitalized and very few reports of deaths resulting from infection.

B. Laboratory Findings

Commercial rapid antigen tests are not optimally sensitive or specific for detection of H5N1 influenza and should not be the definitive test for influenza. More sensitive RT-PCR assays are available through many hospitals and state health departments. Diagnostic yield can be improved by early collection of samples, preferably within 7 days of illness onset. Throat swabs or lower respiratory specimens (such as tracheal aspirate or bronchoalveolar lavage fluid) may provide higher yield of detection than nasal swabs. When highly pathogenic strains, such as H5N1 influenza virus infections, are suspected, extreme care in the handling of these samples must be observed during preliminary testing. Positive samples must then be forwarded to the appropriate public health authorities for further investigation (eg, culture) in laboratories with the adequate level of biosafety (level 3).

► Treatment

Persons with severe illness and confirmed and probable cases with mild disease should receive treatment as soon as

possible. The first-line recommendation is to use the neuraminidase inhibitor oseltamivir, 75 mg orally twice daily for 5 days administered within 48 hours from onset of illness. Longer courses of therapy (eg, 10 days) should be considered in hospitalized patients with severe illness and persistent viral shedding. Data are lacking for use of inhaled zanamivir or peramivir for severe avian influenza. Overall oseltamivir, by modeling, is associated with a 49% reduction in mortality from H5N1 avian influenza virus infections. As with seasonal influenza, enteric oseltamivir is well absorbed in critically ill persons without gastric stasis, known malabsorption, or gastrointestinal bleeding. Daily intravenous peramivir (600 mg, reduced to 200 mg for kidney dysfunction) for a minimum of 5 days and a maximum of 10 or more days (depending on severity of illness) or zanamivir (10 mg inhaled daily for 10 days) may be considered in such patients. Combination therapy with amantadine or rimantadine (in countries where H5N1 influenza virus A strains are likely to be susceptible to adamantanes) may be considered in patients with pneumonia or progressive disease. Resistance of avian H5N1 influenza strains to amantadine and rimantadine is present in most geographic areas. Resistance to neuraminidase inhibitors (oseltamivir, zanamivir, and peramivir) can occur with H5NA and H7N9 avian-infected patients. Successful treatment with administration of convalescent plasma is reported.

► Prevention

The most effective method of prevention is avoidance of exposure. Persons who work with poultry should practice good hand hygiene and use appropriate personal protective equipment. These workers should also be vaccinated against seasonal influenza since this can reduce the likelihood of coinfection with avian and seasonal influenza. Persons should avoid visiting live poultry markets and should avoid contact with ill birds. No risk exists for acquiring avian influenza through the consumption of well-cooked poultry products. The US government bans the importation of poultry from infected areas. Culling of animals has been effective in ending outbreaks of highly pathogenic avian influenza but is difficult with H7-infected poultry because most are asymptomatic. Policies regarding closure of live poultry markets during avian epidemics are controversial.

Persons with exposure should monitor themselves for 10 days after the last known exposure and should seek prompt medical attention if new fever or respiratory symptoms develop. Postexposure prophylaxis is not recommended in persons working with noninfected birds or who used appropriate personal protective equipment while working with infected birds. For persons with exposure to infected persons, postexposure prophylaxis is recommended for household and family members and may be considered for health care personnel with close unprotected contact. Postexposure prophylaxis regimens include 75 mg of oseltamivir orally or 10 mg inhaled zanamivir twice daily for 5 or 10 days from the last known exposure, depending on the length of the exposure. Careful surveillance for human cases and prudent stockpiling of

medications with establishment of an infrastructure for dissemination are essential modalities of control. Non-pharmacologic means of control include masks, social distancing, quarantine, travel limitations, and infrastructure development, particularly for emergency departments.

Vaccines do not provide cross-protection against strains of the H5, H7, and H9 influenza viruses. The US government has prepandemic stockpiles of adjuvanted H5N1 vaccines and H7N9 vaccines that are not available to the public. The highly diverse genetic nature and the rapid evolution of the avian influenza viruses have resulted in the emergence of viruses that are not covered by stockpiled vaccines. The US FDA approved an adjuvanted influenza A (H5N1) monovalent vaccine (Audenz) in January 2020. It is approved for persons 6 months of age and older. Studies investigating vaccine candidates for avian influenza A subtype H7N9 are ongoing.

Because the potential for pandemic influenza for many of the new reassortment viruses is not fully known, continued surveillance is essential, and stockpiling of vaccines, adjuvant, and medications (oseltamivir and zanamivir) is warranted at the public health level.

de Vries RD et al. Avian influenza A virus pandemic preparedness and vaccine development. *Vaccines (Basel)*. 2018;6:E46. [PMID: 30044370]

5. Severe Acute Respiratory Syndrome (SARS-CoV-1)



ESSENTIALS OF DIAGNOSIS

- ▶ Mild, moderate, or severe respiratory illness.
- ▶ Travel to endemic area within 10 days before symptom onset, including mainland China, Hong Kong, Singapore, Taiwan, Vietnam, and Toronto.
- ▶ Persistent fever; dry cough, dyspnea in most.
- ▶ Diagnosis confirmed by antibody testing or isolation of virus.
- ▶ No specific treatment; mortality as high as 14% in clinically diagnosed cases.

► General Considerations

SARS-CoV-1 (previously referred to as “SARS”) is a respiratory syndrome caused by a coronavirus, transmitted through direct or indirect contact of mucous membranes with infectious respiratory droplets. The virus is shed in stools, but the role of fecal-oral transmission is unknown. The natural reservoir appears to be the horseshoe bat (which eats and drops fruits ingested by civets, the earlier presumed reservoir and a likely amplifying host), which can carry a variety of different coronavirus strains.

The earliest cases were traced to a health care worker in Guangdong Province in China in late 2002, with rapid spread thereafter throughout Asia and Canada,

considered a consequence of spread through travel. The last cases were reported in 2004. The 2003 outbreak involved 8098 probable cases from 29 countries, with 774 fatalities. Nine additional cases associated with a research laboratory were reported in China in 2004 with no further cases reported since then. A 29-base pair deletion evolved during the course of human-to-human transmission, and it is thought to be responsible in part for the abeyance of the outbreak.

► Clinical Findings

A. Symptoms and Signs

SARS-CoV-1 is an atypical pneumonia that affects persons in all age groups. Severity ranges from asymptomatic disease to severe respiratory illness. Many subclinical cases probably go undiagnosed. Seasonality, as with influenza, is not established. The incubation period is 2–7 days, and it can be spread to contacts of affected patients for 10 days. The mean time from onset of clinical symptoms to hospital admission is 3–5 days. In all clinical cases, persistent fever is present; chills or rigors (or both), cough, shortness of breath, rales, and rhonchi are the rule. Headache, myalgias, and sore throat are common with watery diarrhea occurring in a subset of patients. Elderly patients may report malaise and delirium, without the typical febrile response.

B. Laboratory Findings and Imaging

Leukopenia (particularly lymphopenia) and low-grade disseminated intravascular coagulation are common. Modest elevations of ALT and creatine kinase are frequently seen. Arterial oxygen saturation less than 95% with associated nonspecific pulmonary infiltrates is evident in 80% of affected individuals. A high-resolution CT scan is abnormal in 67% of patients with initially normal chest radiographs.

Serologic tests, including enzyme immunoassays and fluorescent antibody assays, are available through public health departments at the state level, although seroconversion may not occur until 3 weeks after the onset of symptoms. The detection rates for the virus using conventional RT-PCR are generally low during the first week of illness. Urine, nasopharyngeal aspirate, and stool specimens are positive in 42%, 68%, and 97%, respectively, on day 14 of illness. Viral isolation is technically laborious and time-consuming.

► Complications

ARDS, with extensive bilateral consolidation, occurs in about 16% of patients, and about 20–30% of patients require intubation and mechanical ventilation.

► Treatment

Severe cases require intensive supportive management. Different agents including, lopinavir/ritonavir, ribavirin, interferon, IVIG, and systemic corticosteroids were used during the 2003 epidemic, but the treatment efficacy of these agents remains inconclusive. In vitro studies with

ribavirin show no activity against the virus, and a retrospective analysis of the epidemic in Toronto suggests worse outcomes in patients who received the medication. A 2017 study of alisporivir, a nonimmunosuppressive cyclosporine A analog, alone and in combination with ribavirin, initially showed efficacy *in vitro* but then did not improve outcomes in a mouse model. A meta-analysis studying the use of Chinese herbs failed to show any efficacy in treating SARS-CoV-1. Many promising treatments for SARS-CoV-1 (such as monoclonal antibodies, convalescent sera of convalescent patients, and antivirals) were put on hold when naturally acquired SARS-CoV-1 cases dwindled. However, many of these treatments are now being re-tested and re-purposed for treatment of SARS-CoV-2 infection (please see SARS-CoV-2/COVID-19 for additional details).

► Prognosis

The overall mortality rate of identified cases is about 14%. Poor prognostic factors include advanced age (mortality rate greater than 50% in those over 65 years of age compared with less than 1% for those under 2 years of age), chronic hepatitis B infection treated with lamivudine, high initial or high peak lactate dehydrogenase concentration, high neutrophil count on presentation, diabetes mellitus, acute kidney disease, and low counts of CD4 and CD8 on presentation.

► Prevention

Health care workers engaged in procedures that involve contact with respiratory droplets are at risk. Isolation of high-risk patients is essential, and simple hygienic measures may help reduce transmission.

Control measures include quarantining in the home for high-risk exposed persons. The tourist industry, in particular hotels with attention to hygiene and quarantine, were significant places for control measure in the past outbreak.

Facemasks are useful for preventing hospital acquired infection. Continual reporting of suspected cases is crucial, as is awareness of restrictions on international travel. The most cautious modalities include monitoring for 10 days after the last potential exposure and confinement of recovering patients for a similar interval.

There are two vaccine candidates in early stages of development. One is the 218-amino acid residue receptor-binding domain of SARS, expressed in yeast, and it is called RBD219-N1. The other is a single-plasmid DNA vaccine encoding the spike (S) glycoprotein of SARS; it has been shown to be safe in a phase 1 clinical trial (NCT00099463).

Muth D et al. Attenuation of replication by a 29 nucleotide deletion in SARS-coronavirus acquired during the early stages of human-to-human transmission. *Sci Rep.* 2018;8:15177. [PMID: 30310104]

Sabarimurugan S et al. Comprehensive review on the prevailing COVID-19 therapeutics and the potential of repurposing SARS-CoV-1 candidate drugs to target SARS-CoV-2 as a fast-track treatment and prevention option. *Ann Transl Med.* 2020;8:1247. [PMID: 33178779]

6. Middle East Respiratory Syndrome–Coronavirus (MERS-CoV)



ESSENTIALS OF DIAGNOSIS

- ▶ Mild, moderate, or severe respiratory illness.
- ▶ Travel to endemic area, including Saudi Arabia, United Arab Emirates, Qatar, and Jordan, within 14 days before symptom onset.
- ▶ Contact with camels reported in many cases.
- ▶ Fever, cough, and dyspnea.
- ▶ CDC can assist with RT-PCR.
- ▶ Supportive treatment; mortality 36–45%.

► General Considerations

Middle East respiratory syndrome (MERS) is a syndrome associated with a coronavirus similar to the cause of SARS. Patients with MERS have had a history of residence or travel in the Middle East, in particular Saudi Arabia, or contact with such patients. The virus is transmitted between humans through direct or indirect contact of mucous membranes with infectious respiratory droplets. The virus is shed in stool, but the role of fecal-oral transmission is unknown. The earliest cases were identified in 2012 in the Kingdom of Saudi Arabia, and 75% of all cases have occurred there. Additional cases have occurred throughout the Middle East, Africa, and Europe, with a reported death rate of 36% (<http://www.who.int/emergencies/mers-cov/en/>). Only two cases have ever been identified in the United States; both were reported in 2014 in health care providers who lived and worked in Saudi Arabia. So-called super-spreaders are often responsible for propagating the pathogen in the early stages of an outbreak. It is also recognized more often that asymptomatic cases are frequent, especially among children, and they may contribute to disease transmission.

Person-to-person transmission can occur within families; hospital-associated cases comprise 10–25% of reported infections. The median incubation period is 5 days (range, 2–14) with the mean age of 50 (range 9 months to 99 years) and 65% occurring among men. Over 90% of patients have an underlying medical condition, including diabetes mellitus (68%), hypertension (34%), or chronic heart or kidney disease. Those with diabetes, kidney disease, chronic lung disease, or other immunocompromising conditions likely are at highest risk for severe disease.

Camels (especially female camels) appear to be the principal reservoir, and several studies show that contact with dromedary herds of camels is greater among cases than controls. Raw camel milk is considered a potential source. Persons who work with camels are more likely to have antibody evidence of past infection.

► Clinical Findings

A. Symptoms and Signs

MERS is an acute respiratory syndrome, with the most common symptoms being fever (98%), cough (83%), and

dyspnea (72%). Chills and rigors are common (87%). Gastrointestinal symptoms may occur, with diarrhea being most common (26%), followed by nausea and abdominal pain, and may precede respiratory symptoms. Mild and asymptomatic cases are reported.

B. Laboratory Findings and Imaging

Hematologic findings in the largest series to date include thrombocytopenia (36%), lymphopenia (34%), and lymphocytosis (11%). Moderate elevations in lactate dehydrogenase (49%), AST (15%), and ALT (11%) are recognized. Chest radiograph abnormalities are nearly universal and include increased bronchovascular markings, patchy infiltrates or consolidations, interstitial changes, opacities (reticular and nodular) and pleural effusions, and total lung opacification. Ground-glass opacities and consolidation are most commonly seen. The findings mimic those of many other causes of pneumonia.

Serum serologies and RT-PCR are available through CDC (<https://www.cdc.gov/coronavirus/mers/lab/index.html>). Highest viral loads are found in lower respiratory tract specimens, including bronchoalveolar lavage fluid, sputum, and tracheal aspirates. These samples are preferred for diagnosis. The CDC recommends sending lower respiratory tract specimens, nasopharyngeal and oropharyngeal swabs, and serum for testing. In confirmed cases, serial sample collection (perhaps every 2–4 days) from multiple sites is recommended to increase understanding of virus shedding kinetics. In cases in which symptom onset occurred more than 14 days prior and symptoms are ongoing, serum should be sent to the CDC for serologic testing and the above specimens should be sent for RT-PCR.

C. Case Definition

A patient with severe illness shows the following characteristics: fever (38°C, 100.4°F or higher) and pneumonia or ARDS (based on clinical or radiologic evidence); and either history of travel in or near the Arabian Peninsula within 14 days before symptom onset; or close contact with a symptomatic traveler in whom fever and acute respiratory illness (not necessarily pneumonia) developed within 14 days after traveling in or near the Arabian Peninsula (above); or is a member of a cluster of patients with severe acute respiratory illness (eg, fever and pneumonia requiring hospitalization) of unknown etiology in which MERS-CoV is being evaluated, in consultation with state and local health departments.

In milder illness, patients have fever and symptoms of respiratory illness (not necessarily pneumonia; eg, cough, shortness of breath) and history of having close contact with a confirmed MERS case as well as a history of being in a health care facility (as a patient, worker, or visitor) within 14 days of symptom onset in a country or territory within the Arabian Peninsula in which recent health care-associated cases of MERS have been identified.

Of note, fever may not be present in certain patients, including the very young, elderly persons, immunosuppressed individuals, or those taking certain medications.

► Complications

Respiratory failure is such a common complication that in a series from Saudi Arabia, 89% of patients required intensive care and mechanical ventilation. Patients with MERS-CoV appear to advance faster to respiratory failure than do those with SARS.

► Treatment

Respiratory support is essential. No vaccine or known anti-viral therapy exists to combat MERS. Therapies are adapted from SARS treatments, which include interferons, ribavirin, lopinavir-ritonavir, or mycophenolate mofetil. The use of macrolides is not associated with a reduction in mortality. A small retrospective study found improved survival at 14 days with ribavirin and interferon-alpha but not at 28 days.

► Prognosis

The overall mortality rate of identified cases is about 36%. Factors associated with mortality include the use of corticosteroids and also the use of continuous renal replacement therapy. A set of radiographic criteria (diffuse involvement, fibrosing sequela) are associated with a worse prognosis and the need for intubation. Advanced age is associated with a poor prognosis. Functional outcomes of survivors are similar to those of other non-MERS severe acute respiratory virus illnesses.

► Prevention

Isolation and quarantine of cases is authorized by CDC. Strict infection control measures are essential as well as care and management of household contacts and hospital workers engaged in the care of patients. Travelers to Saudi Arabia (including the many pilgrims to the holy sites) should practice frequent hand washing and avoid contact with those who have respiratory symptoms. Evaluation of patients with suspect symptoms within 14 days of return from Saudi Arabia is essential. Because health care workers engaged in procedures that involve contact with respiratory droplets are at risk, isolation of high-risk patients is essential, as are simple hygienic measures. Limiting the number of hospital contacts and visits is important. Control measures, including quarantining in the home for high-risk exposed persons and the use of facemasks for preventing hospital-acquired infections, are important. Assisting public health authorities with case reporting and surveillance is essential. Postexposure prophylaxis with ribavirin and lopinavir/ritonavir for health care workers is associated with a 40% decrease in the risk of acquiring infection.

Camel workers including slaughterhouse and market workers, veterinarians, and racing personnel should wear facial protection and protective clothing and practice good personal hygiene, including frequent hand washing after touching animals and receive education about the syndrome. Family members of such personnel should not be exposed to work paraphernalia including clothing and shoes and workers should shower at the site of employment rather than the home. Avoidance of direct contact with

camels (who may be asymptomatic but who can transmit the virus through nasal or ocular discharge, milk, urine, and feces) is important. Infected camels should be segregated from other livestock and kept off the market, including their meat products, and buried or destroyed.

Vaccine candidates include subunits to the RBD (receptor binding domain) and spike protein, whole DNA, viral vectors, and inactivated or live attenuated whole virus vaccines.

Alfaraj SH et al. Clinical predictors of mortality of Middle East respiratory syndrome coronavirus (MERS-CoV) infection: a cohort study. *Travel Med Infect Dis.* 2019;39:48. [PMID: 30872071]

Arabi YM et al; Saudi Critical Care Trials Group. Macrolides in critically ill patients with Middle East respiratory syndrome. *Int J Infect Dis.* 2019;81:184. [PMID: 30690213]

Momattin H et al. A systematic review of therapeutic agents for the treatment of the Middle East respiratory syndrome coronavirus (MERS-CoV). *Travel Med Infect Dis.* 2019;30:9. [PMID: 31252170]

Park SY et al. Post-exposure prophylaxis for Middle East respiratory syndrome in healthcare workers. *J Hosp Infect.* 2019; 101:42. [PMID: 30240813]

and 55 commonly cause acute respiratory disease and atypical pneumonia; coinfections or serial infections are documented to occur. Infections are especially severe in Native American children. Adenovirus type 14 is a cause of severe and sometimes fatal pneumonia in those with chronic lung disease but is also seen in healthy young adults and military recruit outbreaks. Viral or bacterial coinfections occur with adenovirus in 15–20% of cases. Pharyngoconjunctival fever is manifested by fever and malaise, conjunctivitis (often unilateral), mild pharyngitis, and cervical adenitis. Epidemic keratoconjunctivitis (transmissible person-to-person, most often types 8, 19, and 37) occurs in adults and is manifested by bilateral conjunctival redness, pain, tearing, and an enlarged preauricular lymph node (multiple types may be involved in a single outbreak). Keratitis may lead to subepithelial opacities (especially with the above types).

Sexually transmitted genitourinary ulcers and urethritis may be caused by types 2, 8, and 37. Adenoviruses also cause acute gastroenteritis (types 40 and 41), mesenteric adenitis, acute appendicitis, rhabdomyolysis, and intussusception. Rarely, they are associated with encephalitis, meningitis, cerebellitis, ARDS, acute flaccid myelitis, and pericarditis. Adenovirus is commonly identified in endomyocardial tissue of patients with myocarditis and dilated cardiomyopathy. Risk factors associated with severity of infection include youth, chronic underlying infections, recent transplantation, and serotypes 5 or 21.

Hepatitis (type 5 adenovirus), pneumonia, and hemorrhagic cystitis (types 11 and 34) tend to develop in infected liver, lung, or kidney transplant recipients, respectively. Disease states that may develop in hematopoietic stem cell transplant patients include hepatitis, pneumonia, diarrhea, hemorrhagic cystitis, tubulointerstitial nephritis, colitis, and encephalitis.

B. Laboratory Findings and Imaging

Antigen detection assays including direct fluorescence assay or enzyme immunoassay are rapid and show sensitivity of 40–60% compared with viral culture (considered the standard). Samples with negative rapid assays require PCR assays or viral cultures for diagnosis. Quantitative real-time rapid-cycle PCR is useful in distinguishing disease from colonization, especially in hematopoietic stem cell transplant patients. Multiplex nucleic acid amplification assays can test for multiple respiratory viruses simultaneously with increased sensitivity. Adenovirus differs from other viral and bacterial respiratory infections seen on chest CT imaging, appearing as a multifocal consolidation or ground-glass opacity without airway inflammatory findings.

C. Treatment & Prognosis

Treatment is symptomatic. Ribavirin or cidofovir is used in immunocompromised individuals with occasional success, although cidofovir is attendant with significant renal toxicity. Brincidofovir, the lipid-conjugated prodrug of cidofovir, has better oral bioavailability, is better tolerated, and achieves higher intracellular concentrations of active drug

ADENOVIRUS INFECTIONS

► General Considerations

At least 60 serotypes of adenovirus are currently described, and these are members of 7 species classified A–G. About half of these subgroups produce a variety of clinical syndromes. Adenoviruses show a worldwide distribution and occur throughout the year. These infections are usually self-limited or clinically inapparent and occur most commonly among infants, young children, and military recruits and appear to be responsible for about 2–7% of childhood viral respiratory infections and 5–11% of viral pneumonia and bronchiolitis. These infections cause particular morbidity and mortality in immunocompromised persons, such as people living with HIV infection and COPD, as well as in patients who have undergone solid organ and hematopoietic stem cell transplantation or cardiac surgery or in those who have received cancer chemotherapy. A few cases of donor-transmitted adenoviral infection have been reported in past years.

Adenoviruses, although a common cause of human disease, also receive particular recognition through their role as vectors in gene therapy and vaccine development.

► Clinical Findings

A. Symptoms and Signs

The incubation period is 4–9 days. Clinical syndromes of adenovirus infection, often overlapping, include the following. The common cold (see Chapter 8) is characterized by rhinitis, pharyngitis, and mild malaise without fever. Conjunctivitis is often present. Nonstreptococcal exudative pharyngitis is characterized by fever lasting 2–12 days and accompanied by malaise and myalgia. Lower respiratory tract infection may occur, including bronchiolitis, suggested by cough and rales, or pneumonia. Types 1, 2, 3, 4, 7,

than cidofovir but currently is only available through compassionate use policies since its primary indicated use remains for Ebola virus infections. IVIG is used in immunocompromised patients and can be used in combination with other therapies, but data are still limited. Reduced immunosuppression is often required. Typing of isolates is useful epidemiologically and in distinguishing transmission from endogenous reactivation. Topical steroids or tacrolimus may be used to treat adenoviral keratoconjunctivitis. The commercially available synthetic corticosteroid mifepristone shows some in vitro activity against adenoviruses. Complications of adenovirus pneumonia in children include bronchiolitis obliterans. Deaths are reported on occasion.

The control of epidemic adenoviral conjunctivitis is often difficult and requires meticulous attention to hand hygiene, use of disposable gloves, sterilization of equipment (isopropyl alcohol is insufficient, recommendations of manufacturers are preferred), cohorting of cases, and furloughing of employees. Treatment with a combination of povidone-iodine 1.0% eyedrops and dexamethasone 0.1% eyedrops four times a day can reduce symptoms and expedite recovery. Prolonged shedding of adenovirus type 55 is reported.

Vaccines are not available for general use. Use of live oral vaccines containing attenuated type 4 and type 7 was reinstated in military personnel in 2013 and has been associated with significant decrease in adenoviral disease.

Fu Y et al. Human adenovirus type 7 infection causes a more severe disease than type 3. *BMC Infect Dis*. 2019;19:36. [PMID: 30626350]

Saha B et al. Recent advances in novel antiviral therapies against human adenovirus. *Microorganisms*. 2020;8:1284. [PMID: 32842697]

OTHER EXANTHEMATOUS VIRAL INFECTIONS

1. *Erythroparvovirus* Infections

Primate *erythroparvovirus* 1, more commonly known as **parvovirus B19**, infects human erythroid precursor cells. It is quite widespread (by age 15 years about 50% of children have detectable IgG), and its transmission occurs through respiratory secretions and saliva, through the placenta (vertical transmission with 30–50% of pregnant women nonimmune), and through administration of blood products. The incubation period is 4–14 days. Chronic forms of the infection can occur. Bocavirus, another erythroparvovirus, is a cause of winter acute respiratory disease in children and adults.

► Clinical Findings

A. Symptoms and Signs

Parvovirus B19 causes several syndromes and manifests differently in various populations.

1. Children—In children, an exanthematous illness (“**fifth disease**,” **erythema infectiosum**) is characterized by a fiery red “slapped cheek” appearance, circumoral pallor, and a

subsequent lacy, maculopapular, evanescent rash on the trunk and limbs. Eosinophilic cellulitis (Well syndrome) is also reported with parvovirus B19, as are microvesicular eruptions and atypical rashes. Parvovirus B19 infection is also one of the most common causes of myocarditis in childhood.

2. Immunocompromised patients—A transient aplastic crisis and pure red blood cell aplasia may occur, although symptoms and signs may be less classic among the immunocompromised populations. Bone marrow aspirates reveal absence of mature erythroid precursors and characteristic giant pronormoblasts. The parvovirus B19 gene is detected in 16–19% of acute leukemia and chronic myeloid leukemia patients.

3. Adults—A limited nonerosive symmetric polyarthritides that mimics lupus erythematosus and rheumatoid arthritis, which may in some cases be a type II mixed cryoglobulinemia, can develop in middle-aged persons (especially women). Rashes, especially facial, are less common in adults.

Chloroquine and its derivatives exacerbate parvovirus B19-associated anemia and are linked with significantly lower hematocrit in hospital admissions in malaria endemic areas. Rare reported presentations include myocarditis with infarction, constrictive pericarditis, chronic dilated cardiomyopathy (although a 2016 analysis from the Netherlands dispute some cardiac findings), uveitis, encephalitis (from India), autoimmune (Hashimoto) thyroiditis, hepatitis and liver failure, pneumonitis, neutropenia, thrombocytopenia, a lupus-like syndrome, glomerulonephritis, CNS vasculitis, papular-purpuric “gloves and socks” syndrome, complications of drug hypersensitivity, and a chronic fatigue syndrome. A subclinical infection is documented among patients with sickle cell disease. Other CNS manifestations of parvovirus B19 include encephalitis, meningitis, stroke (usually in sickle cell anemia patients with aplastic crises), and peripheral neuropathy (brachial plexitis and carpal tunnel syndrome) with occasional chronic residua.

The symptoms of parvovirus B19 infection can mimic those of autoimmune states such as lupus, systemic sclerosis, antiphospholipid syndrome, or vasculitis. A more specific entity named relapsing symmetric seronegative synovitis with edema was reported in two cases to be associated serologically with parvovirus B19 infection.

In pregnancy, premature labor, hydrops fetalis, fetal anemia, and fetal loss are reported sequelae. Pregnant women with a recent exposure or with suggestive symptoms should be tested for the disease and carefully monitored if results are positive.

A serosurvey from France suggests parvovirus B19 infection may occur more commonly in patients with schizophrenia.

Metagenomics studies suggest that parvoviruses are associated with some cases of tubulointerstitial fibrosis.

B. Laboratory Findings

The diagnosis is clinical (Table 32–2) but may be confirmed by either an elevated titer of IgM anti-parvovirus B19 antibodies in serum or with PCR in serum or

bone marrow. By the time common presenting symptoms manifest, in particular a rash or polyarthropathy in an immunocompetent patient, the viremia may have cleared but IgM antibodies are likely present. In immunocompromised patients, RT-PCR is the optimal test. Autoimmune antibodies (antiphospholipid and antineutrophil cytoplasmic antibodies) can be present and are thought to be a consequence of molecular mimicry. False-positive serologies also occur in the presence of recent IVIG and anti-B-cell therapy. Also, remnant parvovirus B19, from tissue and serum, is thought to explain some false-positive findings. Assays on marrow tissue are indicated only if a marrow is deemed necessary for other hematologic reasons.

Treatment

Treatment in healthy persons is symptomatic (NSAIDs are used to treat arthralgias, and transfusions are used to treat transient aplastic crises). In immunosuppressed patients including those with HIV, IVIG is very effective in the short-term reduction of anemia. Relapses tend to occur about 4 months after administration of IVIG. There is no reduction in encephalitic complications with IVIG. Intrauterine blood transfusion can be considered in severe fetal anemia, although such transfusions have been linked to impaired neurologic development.

Prevention & Prognosis

Several nosocomial outbreaks are documented. In these cases, standard containment guidelines, including hand washing after patient exposure and avoiding contact with pregnant women, are paramount. Among infected, pregnant women, the presence of hydrops is associated with a poor prognosis. Serologic data show that day-care attendants are at higher risk for infection and need practice hygienic principles in particular.

Because transfusion-transmitted parvovirus is very rare, blood banks do not routinely screen for parvovirus in the United States or abroad. Most infected donor patients have concomitant antibodies, most recipients have had prior parvovirus infection, and the levels of viremia are considered too low in infected patients to transmit the virus. Transfusion specialists recommend DNA screening of vulnerable patients after transfusion.

The prognosis is generally excellent in immunocompetent individuals. In immunosuppressed patients, persistent anemia may require prolonged transfusion dependence. Remission of parvovirus B19 infection in AIDS patients may occur with ART, though the immune reconstitution inflammatory syndrome is also reported.

Telbivudine, a thymidine analog used in hepatitis B virus infection, appears to show some in vitro activity, in particular with myocarditis, suggesting a potential future commercial role for this compound in parvovirus B19 infections.

Roediger B et al. An atypical parvovirus drives chronic tubulointerstitial nephropathy and kidney fibrosis. *Cell*. 2018;175:530. [PMID: 30220458]

Romero Starke K et al. Are daycare workers at a higher risk of parvovirus B19 infection? A systematic review and meta-Analysis. *Int J Environ Res Public Health*. 2019;16:E1392. [PMID: 30999694]

Sim JY et al. Human parvovirus B19 infection in patients with or without underlying diseases. *J Microbiol Immunol Infect*. 2019;52:534. [PMID: 31257106]

2. Poxvirus Infections

Among the poxviruses causing disease in humans, the following are the most clinically important: variola/vaccinia, molluscum contagiosum, orf and paravaccinia, and monkeypox.

1. Variola/vaccinia—Smallpox (caused by the variola virus) was a highly contagious disease associated with high mortality and disabling sequelae. Its manifestations include severe headache, acute onset of fever, prostration, and a rash characterized by uniform progression from macules to papules to firm, deep-seated vesicles or pustules. The synchronous progression in smallpox readily differentiates lesions from those of varicella (see also Chapter 6).

Complications of smallpox include bacterial superinfections (cellulitis and pneumonia), encephalitis, and keratitis with corneal ulcerations (risk factor for blindness). Effective vaccination led to its global elimination by 1979 and routine vaccination stopped in 1985. Recommendations to destroy remaining samples of this virus have not been acted upon thus far, and significant concern exists for potential misuse of these repositories in military or terrorist activities.

Smallpox should be considered, in concordance with the CDC Smallpox Response Plan (<https://www.cdc.gov/smallpox/bioterrorism-response-planning/community/index.html>), in any patient with fever and a characteristic rash for which other etiologies—such as herpes infections (eczema herpeticum may be differentiated from suspect smallpox by appropriate serologic stains and clinical appearance), erythema multiforme, drug reactions, or other infections—are unlikely. Patients with suspected infection should be placed in airborne and contact isolation and the official agency contacted (CDC Poxvirus and Rabies Branch help desk may be reached at 404-639-4129 and the Director's Emergency Operation Center at 770-488-7100).

A needle-stick injury case of vaccinia virus infection reported in 2019 from California was treated with the p37 inhibitor tecovirimat and vaccinia immune globulin intravenous (VIGIV) and resolution of a necrotic finger lesion was prolonged (94 days).

Guidelines regarding smallpox vaccination are available at <https://www.cdc.gov/smallpox/vaccine-basics/index.html>.

2. Molluscum contagiosum—Molluscum contagiosum is caused by a molluscipox virus that may be transmitted sexually or by other close contact. The disease is manifested by pearly, raised, umbilicated skin nodules sparing the palms and soles. Keratoconjunctivitis can occur. Most ocular lesions are typical umbilicated dome-shaped lesions, but a variety of atypical ocular lesions are reported often in

immunocompetent patients, more often in females and young adults (mean age 19).

There may be an association with atopic dermatitis or eczema. Marked and persistent lesions in AIDS patients respond readily to combination ART. Treatment options include destructive therapies (curettage, cryotherapy, cantharidin, 10–15% hydrogen peroxide, 10% potassium hydroxide, and keratolytics [ingenol mebutate and SB206/berdazimer sodium gel are under study], among others), immunomodulators (imiquimod, cimetidine, cantharidin, tuberculin-purified protein derivatives [PPDs], and *Candida* antigen), and antiviral agents (topical cidofovir is effective anecdotally in refractory cases; brincidofovir is approved for the treatment of Ebola but is still off-label for molluscum contagiosum, where it shows some efficacy). No treatment is uniformly effective, and multiple courses of therapy are often needed. One meta-analysis recommends natural resolution of lesions if normal immunity can be restored.

3. Orf and paravaccinia—Orf (contagious pustular dermatitis, or ecthyma contagiosa) and paravaccinia (milker's nodules) are occupational diseases acquired by contact with sheep/goats and cattle, respectively. Household meat processing and animal slaughter have been implicated as risk factors. A new poxvirus akin to parapoxviruses was reported in 2015 in two patients from rural Tennessee and Missouri (the latter had also traveled to Tanzania). Orf is a common infection in sheep, goats, and deer. Thus, it is found worldwide, and farmers, veterinarians, and hunters are considered high-risk populations. It progresses through six clinically distinct dermatologic stages and lesions usually heal in 3–6 weeks without scarring. The use of nonporous gloves for persons handling animals is recommended, especially if the persons are immunosuppressed. Molecular tests are used to confirm clinical diagnosis. Although there is no specific treatment, Orf anecdotally responds to imiquimod. A live vaccine is available for animals, and the orfvirus, which has immunomodulatory properties, is increasingly used as a vector and as an oncolytic agent in human vaccine trials.

4. Monkeypox—First identified in 1970, monkeypox is enzootic in the rain forests of equatorial Africa and presents in humans as a syndrome similar to smallpox. The incubation period is about 13 days (range, 6–28 in one Central African Republic outbreak) and limited person-to-person spread occurs. Mortality rates vary from 3% to 11% depending on the immune status of the patient. Secondary attack rates appear to be about 10%. Since 2017, confirmed cases of monkeypox have occurred in Cameroon, Central African Republic, Côte d'Ivoire, Democratic Republic of the Congo, Republic of the Congo, Gabon, Liberia, Nigeria (where cases occurred after a 40-year hiatus), Sierra Leone, and South Sudan. Risk factors identified from the Democratic Republic of Congo include being bitten by rodents, working as a hunter, and being male over 18 years of age. The giant pouched rat is a particular reservoir for disease in Central Africa.

Confusion with smallpox and varicella occurs; however, both lymphadenopathy (seen in up to 90% of unvaccinated

persons) and a febrile prodrome are prominent features in monkeypox infection. The monkeypox rash is distinguished by its deep-seated and well-circumscribed nature, lesions at the same stage of development (unlike varicella but like smallpox), and its centrifugal progression (including palms and soles). Suspected cases should be placed on standard, contact, and droplet precautions; local and state public health officials and the CDC should be notified for assistance with confirmation of the diagnosis (by electron microscopy, viral culture, ELISA, PCR, and a GeneXpert assay referred to as MPX/OPX [monkeypox/orthopox]). There are no standard or optimized guidelines for the clinical management of monkeypox. Cidofovir is effective in vitro against monkeypox, and its less toxic prodrug brincidofovir may be useful as well. Vaccinia immune globulin can be used in selected cases.

Other general precautions that should be taken are avoidance of contact with rodents from endemic areas (whose illness is manifested by alopecia, rash, and ocular or nasal discharge), appropriate care and isolation of humans exposed to such animals within the prior 3 weeks, and veterinary examination and investigation of suspect animals through health departments. Vaccinia immunization is effective against monkeypox and is recommended for those involved in the investigation of the outbreak and for health care workers caring for those infected with monkeypox if no contraindication exists (outlined above). Postexposure vaccination is also advised for documented contacts of infected persons or animals. US federal agencies prohibit the importation of African rodents.

5. Novel orthopoxviruses—Two cases of a novel orthopoxvirus were identified in the country of Georgia in 2013 with a third diagnosed serologically from 2010. All cases had animal contact, two had cattle contact, and serologic data showed possible associations with rodents and shrews as well as cattle. None had been vaccinated for smallpox. Another novel orthopoxvirus was identified in a patient who had undergone kidney transplantation in North America in 2015. The seroprevalence to orthopoxviruses is high in veterinary workers and those with cat exposures.

Centers for Disease Control and Prevention (CDC). Updated interim CDC guidance for use of smallpox vaccine, cidofovir, and vaccinia immune globulin (VIG) for prevention and treatment in the setting of an outbreak of monkeypox infections. <http://www.cdc.gov/ncidod/monkeypox/treatment-guidelines.htm>

Delaune D et al. Drug development against smallpox: present and future. *Antimicrob Agents Chemother*. 2020;64:e01683. [PMID: 31932370]

Durski KN et al. Emergence of monkeypox—west and central Africa, 1970–2017. *MMWR Morb Mortal Wkly Rep*. 2018;67:306. [PMID: 29543790]

Meyer H et al. Smallpox in the post-eradication era. *Viruses*. 2020;12:138. [PMID: 31991671]

Teixidó C et al. Efficacy and safety of topical application of 15% and 10% potassium hydroxide for the treatment of molluscum contagiosum. *Pediatr Dermatol*. 2018;35:336. [PMID: 29479727]

Wang R et al. Orf virus: a promising new therapeutic agent. *Rev Med Virol*. 2019;29:e2013. [PMID: 30370570]

VIRUSES & GASTROENTERITIS

Viruses are responsible for at least 30–40% of cases of infectious diarrhea in the United States. These agents include rotaviruses; caliciviruses, including noroviruses such as Norwalk virus; astroviruses; enteric adenoviruses; and, less often, toroviruses, coronaviruses, picornaviruses (including the Aichi virus), and pestiviruses. Rotaviruses and noroviruses are responsible for most nonbacterial cases of gastroenteritis.

Rotaviruses are reoviruses with eight species and significant animal reservoirs and are associated with significant morbidity and mortality. Each year, over 200,000 children die of rotavirus infection worldwide. Children aged 6 months to 2 years are the most affected, although adults are affected occasionally as well. By age 5, virtually every child has been infected with this pathogen. The diverse set of rotaviruses (classified by glycoproteins and protease-sensitive proteins [G-type and P-type antigens], which segregate independently) results in a constellation of phenotypes, although only about four of these are responsible for over 90% of disease. Rotavirus infections follow an endemic pattern, especially in the tropics and low-income countries, but they peak during the winter in temperate regions. The virus is transmitted by fecal-oral route and can be shed in feces for up to 3 weeks in severe infections. In outbreak settings (eg, day care centers), the virus is ubiquitously found in the environment, and secondary attack rates are between 16% and 30% (including household contacts). Nosocomial outbreaks are reported.

The disease is usually mild and self-limiting. A 2- to 3-day prodrome of fever and vomiting is followed by non-bloody diarrhea (up to 10–20 bowel movements per day) lasting for 1–4 days. It is thought that systemic disease occurs rarely, and unusual reported presentations include cerebellitis and pancreatitis. Patients with gastroenteritis are not routinely tested for rotavirus because the results do not alter treatment. Oral and intravenous rehydration solutions are the primary treatment options, but effective adjunctive therapies include specific probiotics (eg, *Lactobacillus GG* or *Saccharomyces boulardii*), nitazoxanide, diosmectite, or racecadotril. Adjunctive therapies such as oral odansetron shorten the median duration of diarrhea and hospitalization. Local intestinal immunity gives protection against successive infection.

Vaccines have been highly successful in reducing the global burden of rotavirus. Four oral, live, attenuated rotavirus vaccines—Rotarix (derived from a single common strain of human rotavirus), RotaTeq (a reassorted bovine-human rotavirus), Rotavac (naturally occurring bovine-human reassortant neonatal G9P, also called 116E), and RotaSiil (bovine-human reassortant with human G1, G2, G3 and G4 bovine UK G6P[5] backbone)—are available internationally and WHO prequalified. All four vaccines are considered highly effective in preventing severe gastrointestinal disease. In the United States, two rotavirus vaccines have been approved since 2006: RotaTeq (given at 2, 4, and 6 months of age) and a live, oral attenuated monovalent human rotavirus vaccine (HRV, Rotarix or RV1; given at 2 and 4 months of age). One advantage of these vaccines

is the evidence of heterotypic immunity (prevention against rotavirus strains not included in the vaccine). Accordingly, some data from the Americas suggest that rotavirus vaccination confers herd immunity to children under 1 year of age. Vaccine policies are estimated to potentially prevent 600,000 deaths in 58 of the world's poorest GAVI (formerly Global Alliance for Vaccines and Immunizations)—supported countries between 2018 and 2019.

Vaccine coverage is inadequate in the United States for rotavirus (75.3% in the 2017 National Immunization Study), particularly among the poor. National immunization programs of over 80 countries include rotavirus vaccine, and the different rotavirus vaccines are available commercially in 100 countries.

With the control of rotavirus, **noroviruses**, such as Norwalk virus (one of a variety of small round viruses divided into 6 genogroups [3 causing disease in man] and at least 25 genotypes), are now *the major cause of diarrhea globally*. Noroviruses are a leading cause of food-borne disease in the United States (with food handlers largely responsible and associated foods most often leafy vegetables, fruits, nuts, and mollusks) and are significantly associated with military deployment as well as travel-associated and nosocomial infections.

Norovirus gastroenteritis is responsible for nearly 700 million infections globally annually and up to 20% of all diarrhea in both children and adults, with an estimated 900 deaths annually in the United States (primarily among older adults) and 200,000 deaths globally. The efficacy of the rotavirus vaccination has increased the percentage of gastroenteritis caused by norovirus. The noroviruses appear to evolve by antigenic drift (similar to influenza). While 90% of young adults show serologic evidence of past infection, no long-lasting protective immunity develops, and reinfections are common.

Outbreak environments include long-term care facilities (nursing homes in particular), restaurants, hospitals, schools, day care centers, vacation destinations (including cruise ships), and military bases. Persons at particular risk are younger individuals, older adults, those who are institutionalized, and those who are immunosuppressed. Although transmission is usually fecal-oral, airborne, person-to-person, and water-borne transmission are also documented. A short incubation period (24–48 hours), a short symptomatic illness (12–60 hours, but up to 5 days in hospital-associated cases), a high frequency (greater than 50%) of vomiting, and absence of bacterial pathogens in stool samples are highly predictive of norovirus gastroenteritis.

RT-PCR of stool samples is used for diagnostic and epidemiologic purposes. Several licensed multiple pathogen platform assays are available, but they are expensive and interpretation of the cause of illness in a given patient may be difficult. Treatment options are similar to rotavirus (see above) and rely mostly on oral and intravenous rehydration. Deaths are rare in the developed world, and the more common associated diseases are aspiration pneumonia, septicemia, and necrotizing enterocolitis.

Outbreak control for both rotavirus and norovirus infections include strict adherence to general hygienic measures. Despite the promise of alcohol-based sanitizers

for the control of pathogen transmission, such cleansers may be relatively ineffective against the noroviruses compared with antibacterial soap and water, reinforcing the need for new hygienic agents against this prevalent group of viruses. Cohorting of sick patients, contact precautions for symptomatic hospitalized patients, and proper decontamination procedures are crucial. Symptomatic staff should be excluded from work until symptom resolution (or 48–72 hours after this for norovirus disease).

Burnett E et al. Real-world effectiveness of rotavirus vaccines, 2006–19: a literature review and meta-analysis. *Lancet Glob Health.* 2020;8:e1195. [PMID: 32827481]

Leroux-Roels G et al. Safety and immunogenicity of different formulations of norovirus vaccine candidate in healthy adults: a randomized, controlled, double-blind clinical trial. *J Infect Dis.* 2018;217:597. [PMID: 29140444]

Netzler NE et al. Norovirus antivirals: where are we now? *Med Res Rev.* 2019;39:860. [PMID: 30584800]

occur in less than 10% of patients. Most patients are ill for 4–6 days.

4. Aseptic meningitis (A and B) and other neurologic syndromes—Fever, headache, nausea, vomiting, stiff neck, drowsiness, and CSF lymphocytosis without chemical abnormalities may occur, and pediatric clusters of group B (especially B5) meningitis are reported. Focal encephalitis and transverse myelitis are reported with coxsackievirus group A and acute flaccid myelitis with group B in India. Disseminated encephalitis occurs after group B infection, and acute flaccid myelitis is reported with both coxsackievirus groups A and B.

5. Acute nonspecific pericarditis (B types)—Sudden onset of anterior chest pain, often worse with inspiration and in the supine position, is typical. Fever, myalgia, headache, and pericardial friction rub appear early and these symptoms are often transient. Evidence for pericardial effusion on imaging studies is often present, and the occasional patient has a paradoxical pulse. Electrocardiographic evidence of pericarditis is often present. Relapses may occur.

6. Myocarditis (B1–5)—Heart failure in the neonatal period secondary to *in utero* myocarditis and over 20% of adult cases of myocarditis and dilated cardiomyopathy are associated with group B (especially B3) infections.

7. Hand, foot, and mouth disease (A5, 6, 10, 12, and 16, B5)—This disease can be epidemic. It is characterized by stomatitis, a vesicular rash on hands and feet (Figure 32–7), nail dystrophies, and onychomadesis (nail shedding), with some cases showing higher fevers, long duration, and more severe skin manifestations. Enteroviruses 71 and 33 are also causative agents, the former of usually more severe disease. A16 disease is usually mild. A6 may be atypical but is usually self-limited. Rare fatalities are reported among surveillance programs in China where recombinant patterns between coxsackieviruses and echoviruses are reported.

ENTEROVIRUSES THAT PRODUCE SEVERAL SYNDROMES

The most famous enterovirus, the poliomyelitis virus, is discussed above under Major Vaccine-Preventable Viral Infections. Other clinically relevant enteroviral infections are discussed in this section.

1. Coxsackievirus Infections

Coxsackievirus infections cause several clinical syndromes. As with other enteroviruses, infections are most common during the summer. Two groups, A and B, are defined either serologically or by mouse bioassay. There are more than 50 serotypes.

► Clinical Findings

A. Symptoms and Signs

The clinical syndromes associated with coxsackievirus infection are summer gripe; herpangina; epidemic pleurodynia; aseptic meningitis and other neurologic syndromes; acute nonspecific pericarditis; myocarditis; hand, foot, and mouth disease; epidemic conjunctivitis; and other syndromes.

1. Summer gripe (A and B)—A febrile illness, principally of children, summer gripe usually lasts 1–4 days. Minor upper respiratory tract infection symptoms are often present.

2. Herpangina (A2–6, 10; B3)—There is sudden onset of fever, which may be as high as 40.6°C, sometimes with febrile convulsions. Other symptoms are headache, myalgia, and vomiting. The sore throat is characterized early by petechiae or papules on the soft palate that ulcerate in about 3 days and then heal. Treatment is symptomatic.

3. Epidemic pleurodynia (Bornholm disease) (B1–5)—Pleuritic pain is prominent. Tenderness, hyperesthesia, and muscle swelling are present over the area of diaphragmatic attachment. Other findings include headache, sore throat, malaise, nausea, and fever. Orchitis and aseptic meningitis



▲ Figure 32–7. Typical flat, gray, oval vesicular lesions on the ventral hand and fingers. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

8. Epidemic conjunctivitis—As with enterovirus 70, the A24 variant of coxsackievirus is associated with acute epidemic hemorrhagic conjunctivitis in tropical areas with outbreaks reported in southern China, Pakistan, southern Sudan, the Comoros, Uganda, Cuba, and Thailand. It is also reported as a cause of corneal endothelitis after cataract surgery.

9. Other syndromes associated with coxsackievirus infections—These include rhabdomyolysis, fulminant neonatal hepatitis (occurs rarely), pancreatitis with concomitant hepatitis and myocarditis (A4), glomerulopathy (group B infections), onychomadesis (B1), neonatal hemophagocytic lymphohistiocytosis (B1), types 1 and 2 diabetes mellitus (mainly group B infections), and thyroid disease (group B4), although definitive causality is not established. A pathogenic role in primary Sjögren syndrome and acute myocardial infarction has also been proposed for group B coxsackievirus infections. A report of confirmed infective endocarditis due to coxsackievirus B2 in a patient with a prosthetic cardiac patch used in repair of a child with complete atrial ventricular septal defect suggests that viral etiologies of culture-negative infective endocarditis should be considered even in cases of cardiac surgery.

B. Laboratory Findings

Routine laboratory studies show no characteristic abnormalities. Neutralizing antibodies appear during convalescence. The virus may be isolated from throat washings or stools inoculated into suckling mice. Viral culture is expensive, labor intensive, and requires several days for results. A PCR test for enterovirus RNA is available and, although it cannot identify the serotype, may be useful, particularly in cases of meningitis.

► Treatment & Prognosis

Treatment is symptomatic. Except for meningitis, myocarditis, pericarditis, diabetes, and rare illnesses such as pancreatitis or poliomyelitis-like states, the most common syndromes caused by coxsackieviruses are benign and self-limited. Two controlled trials showed a potential clinical benefit with pleconaril for patients with enteroviral meningitis although the compassionate use of this medication has stopped (clinicians can contact Schering Plough for updates). There are anecdotal reports of success with IVIG in severe disease. Vaccines against the most common etiologic agents in a given country have been developed, but simultaneous circulation of more than one virus make coxsackievirus vaccines based on a single agent relatively ineffective.

Esposito S et al. Hand, foot and mouth disease: current knowledge on clinical manifestations, epidemiology, aetiology and prevention. Eur J Clin Microbiol Infect Dis. 2018;37:391. [PMID: 29411190]

2. Echovirus Infections

Echoviruses are enteroviruses that produce several clinical syndromes, particularly in children. Infection is most common during summer. Among reported specimens, death

ensues in about 3%. Males younger than 20 years are more commonly infected than other persons.

Over 30 serotypes of echoviruses are recognized and the most common serotypes for disease are A types 6, 9, 11, 19, 29, 30, and 33 as well as C99. Most can cause aseptic meningitis, which may be associated with a rubelliform rash. Transmission is primarily fecal-oral. Hand washing is an effective control measure in outbreaks of aseptic meningitis. Outbreaks related to fecal contamination of water sources, including drinking water and swimming and bathing pools, were reported previously.

Besides meningitis, other conditions associated with echoviruses range from common respiratory diseases and epidemic diarrhea to myocarditis, a hemorrhagic obstetric syndrome, keratoconjunctivitis, severe hepatitis with coagulopathy, leukocytoclastic vasculitis, encephalitis with sepsis, interstitial pneumonitis, pleurodynia, hemophagocytic syndromes (in children with cancer), sudden deafness, encephalitis, acute flaccid myelitis (a leading cause in India), optic neuritis, uveitis, and septic shock. Echoviruses and enteroviruses are also a common cause of nonspecific exanthems.

As with other enterovirus infections, diagnosis is best established by correlation of clinical, epidemiologic, and laboratory evidence. Cytopathic effects are produced in tissue culture after recovery of virus from throat washings, blood, or CSF. An enterovirus PCR of the CSF can assist in the diagnosis and is associated with a shorter duration of hospitalization in febrile neonates. Fourfold or greater rises in antibody titer signify systemic infection.

Treatment is usually symptomatic, and the prognosis is excellent, though there are reports of mild paralysis after CNS infection. In vitro data suggest some role for amantadine or ribavirin, but clinical studies supporting these findings are not available.

From a public health standpoint, clustered illnesses, such as among travelers swimming in sewage-infested seawater, suggest point-source exposure. Prevention of fecal-oral contamination and maintenance of pool hygiene through chlorination and pH control are important public health control measures.

Broberg EK et al; The Eu/Eea Member State Contributors. Upsurge in echovirus 30 detections in five EU/EEA countries, April to September, 2018. Euro Surveill. 2018;23:1800537. [PMID: 30401013]

Zhang J et al. Identification of a new recombinant strain of echovirus 33 from children with hand, foot, and mouth disease complicated by meningitis in Yunnan, China. Virol J. 2019;16:63. [PMID: 31068194]

3. Enteroviruses 68, 70, 71, & Related Agents

Enteroviruses are nonenveloped, single-stranded viruses in the *Picornaviridae* family. They are divided into 12 species (A to L; human enteroviruses include species A to D). Several distinct clinical syndromes are described in association with enteroviruses.

Enterovirus D68 (EV-D68) is a unique enterovirus that shares epidemiologic characteristics with human rhinovirus and is typically associated with respiratory illness.

Several clusters are reported from the Netherlands, Japan, the Philippines, and Thailand. An outbreak throughout the United States was reported during 2014–2015. The outbreak was also associated with cases of acute flaccid myelitis but not definitively linked thus far. The virus is implicated also in aseptic meningitis and encephalitis.

Enterovirus 70 (EV-A70), a ubiquitous virus and responsible for abrupt bilateral eye discharge and subconjunctival hemorrhage with occasional systemic symptoms, is most commonly associated with acute hemorrhagic conjunctivitis.

Enterovirus 71 (EV-A71) almost always occurs in the Asia-Pacific region (but with reports from the United States since the 1980s) and is associated with (1) hand, foot, and mouth disease, which can be severe or even fatal; (2) herpangina; (3) a form of epidemic encephalitis associated on occasion with pulmonary edema; and (4) acute flaccid myelitis mimicking poliomyelitis (see separate section on acute flaccid myelitis).

Human enteroviruses are neurotropic. They may have a role in amyotrophic lateral sclerosis. EV-D68 has been reported in a case of fatal meningitis/encephalitis. A number of nonpolio type C enteroviruses are associated with polio-like syndromes, and surveillance for these is most active in China. Enterovirus infection of the pancreas can trigger cell-mediated autoimmune destruction of beta cells resulting in diabetes. Enterovirus myocarditis can be a serious infection in neonates, complicated by cardiac dysfunction and arrhythmias. An association with hemophagocytosis is also reported.

Mortality is especially high in EV-A71-associated brainstem encephalitis, which is often complicated by pulmonary edema, particularly when it occurs in children younger than 5 years. A complication is autonomic nervous system dysregulation, which may precede the pulmonary edema. Because of lower herd immunity, hand, foot, and mouth disease tends to infect children under age 5 in nonendemic areas. Clinical and epidemiologic findings aided by isolation of the suspect agent from conjunctival scraping for EV-A70; vesicle swabs, body secretions, or CSF for EV-A71; and respiratory secretions for D68 facilitate diagnosis of these enteroviral entities. Enzyme immunoassays and complement fixation tests show good specificity but poor sensitivity (less than 80%). RT-PCR may increase the detection rate in enterovirus infections and is useful in the analysis of CSF samples among patients with meningitis and of blood samples among infants with a sepsis-like illness.

Treatment of these entities remains largely symptomatic. A study in China showed that recombinant human interferon-alpha1b in EV-A71-associated hand, foot, and mouth disease was associated with decreased fever duration, healing time of typical skin or oral mucosal lesions, and EV-A71 viral load. There is anecdotal success in managing myocarditis with immunoglobulins.

The major complication associated with EV-A70 is the rare development of an acute neurologic illness with motor paralysis akin to poliomyelitis. Treatment of acute flaccid myelitis related to EV-A71 with IVIG does not appear to improve neurologic outcomes. Attention-deficit with

hyperactivity occurs in about 20% with confirmed infection.

EV-D68 requires supportive care with particular attention to respiratory support. The CDC's National Enterovirus Surveillance System should receive reports of disease at <https://www.cdc.gov/surveillance/ness/ness-sites.html>.

Household contacts, especially children under 6 months of age, are at particular risk for EV-A71 acquisition. A commercial disinfectant, Virkon S at 1–2% application, appears to reduce infectivity of fomites. A stage-based supportive treatment for EV-A71 infections, recognizing the potential for late-onset CNS disease and cardiopulmonary failure is important. There is no commercially available EV-A71 vaccine in the United States, although vaccines produced in China appear to be successful against EV-A71-associated hand, foot, and mouth disease and herpangina. Decreases in antibody titers suggest booster doses of these vaccines may be needed.

Enterovirus 72 (EV-A72) is another term for hepatitis A virus (see Chapter 16). **Enterovirus EV-A104** is related to rhinoviruses and associated with respiratory illness in reports from Italy and Switzerland.

Hu YL et al. Current status of enterovirus D68 worldwide and in Taiwan. *Pediatr Neonatol*. 2020;61:9. [PMID: 31706947]
Rodriguez-Calvo T. Enterovirus infection and type 1 diabetes: unraveling the crime scene. *Clin Exp Immunol*. 2019;195:15. [PMID: 30307605]

4. Human Parechovirus Infection

Human parechovirus is classified among 19 genotypes among a distinct genus of picornaviruses and causes a wide variety of disease in humans, especially in infants. The pathogen mainly affects small children during the summer and early fall, although disease can also occur in older adults. Cases are reported worldwide. Virus type A3 is the most commonly reported isolate in the United States. In a recent Chinese study of children with acute gastroenteritis, 12% tested positive for parechovirus A and the most common genotype was A1b. Clinical presentation is mainly driven by gastrointestinal and respiratory illness, although otitis, neonatal sepsis, fever without a detectable source, gastroenteritis, flaccid paralysis, myalgias (which may be epidemic), diffuse maculopapular and palmar-plantar rashes, aseptic meningitis, intracranial hemorrhage, seizures, pericarditis, and an acute disseminated encephalitis are described in the literature.

Type A6 typically affects individuals older than 20 years while type A3 is responsible for meningitis/encephalitis, neonatal sepsis (13% of late-onset neonatal sepsis [between 4 and 120 days of life] in one series was due to parechovirus) and was reported in association with necrotizing enterocolitis and hepatitis. It is the most common cause of neonatal meningitis and is the picornavirus most often found in CSF samples of CNS-related infections in very young children. The encephalitis can be severe, and the Guillain-Barré syndrome is also reported with parechovirus type A6. CSF parameters include a normal count in over 90% and an abnormal protein in less than 50%. CNS

infection may be seen with virus type A4 as well. Respiratory and gastrointestinal illnesses are seen with types A4–A6, A10, A13, and A15.

Treatment is largely supportive and rapid identification of the viral antigen by PCR in stools, respiratory samples, and CSF may decrease use of unnecessary antibiotics and shorten hospital stay, although current PCR assays are not always sufficiently sensitive to exclude parechoviruses. Intravenous immunoglobulin was anecdotally successful in one case of parechovirus dilated cardiomyopathy and maternal antibodies to parechovirus type 3 are protective. Reported complications of neonatal cerebral infections include learning disabilities, epilepsy, and cerebral palsy. Because intrafamilial transmission is well documented, diagnosis may help isolate the affected children. Also, diagnosis may prevent the excessive use of antibiotics.

Abedi GR et al. Enterovirus and parechovirus surveillance—United States, 2014–2016. MMWR Morb Mortal Wkly Rep. 2018;67:515. [PMID: 29746455]

Kabuga AI et al. Human parechovirus are emerging pathogens with broad spectrum of clinical syndromes in adults. J Med Virol. 2020. [Epub ahead of print] [PMID: 32761910]

Zhu YN et al. Prevalence and molecular characterization of parechovirus A in children with acute gastroenteritis in Shenzhen, 2016–2018. Arch Virol. 2020;165:1377. [PMID: 32296995]

individual, the feces enter the bloodstream when the person scratches the itching wound. Dry, infectious louse feces may also enter via the respiratory tract. Cases can be acquired by travel to pockets of infection (eg, central and northeastern Africa, Central and South America). Outbreaks have been reported from Peru, Burundi, Ethiopia, Turkey, and Russia and are associated with migration of peoples as well as with refugee camps where crowding and poor hygiene may occur. Because of aerosol transmissibility, *R prowazekii* is considered a possible bioterrorism agent. In the United States, cases occur among the homeless, refugees, and the unhygienic, most often in the winter.

R prowazekii can survive in lymphoid and adipose (in endothelial reservoirs) tissues after primary infection, and years later, produce recrudescence of disease (**Brill-Zinsser disease**) without exposure to infected lice. This phenomenon can serve as a point source for future outbreaks.

An extrahuman reservoir of *R prowazekii* in the United States is flying squirrels, *Glaucomys volans*. Transmission to humans can occur through their ectoparasites, known as sylvatic typhus, usually causing atypical mild disease. Foci of sylvatic typhus are found in the eastern United States and are reported to occur in Brazil, Ethiopia, and Mexico.

RICKETTSIAL DISEASES

TYPHUS GROUP

1. Epidemic (Louse-Borne) Typhus



ESSENTIALS OF DIAGNOSIS

- ▶ Prodrome of headache, then chills and fever.
- ▶ Severe, intractable headaches, prostration, persistent high fever.
- ▶ Macular rash appearing on days 4–7 on the trunk and in the axillae, spreading to the rest of the body but sparing the face, palms, and soles.
- ▶ Diagnosis confirmed by complement fixation, microagglutination, or immunofluorescence.

General Considerations

Epidemic louse-borne typhus is caused by *Rickettsia prowazekii*, an obligate parasite of the body louse *Pediculus humanus* (other lice were thought not to contribute although a 2018 report from Turkey suggests *P humanus capitatus* may transmit *R prowazekii*) (Table 32–3). Transmission is favored by crowded, unsanitary living conditions, famine, war, or any circumstances that predispose to heavy infestation with lice. After biting a person infected with *R prowazekii*, the louse becomes infected by the organism, which persists in the louse gut and is excreted in its feces. When the same louse bites an uninfected

Clinical Findings

A. Symptoms and Signs

Prodromal malaise, cough, headache, backache, arthralgia, myalgia, and chest pain begin after an incubation period of 10–14 days, followed by an abrupt onset of chills, high fever, and prostration, with flu-like symptoms progressing to delirium and stupor. The headache is severe, and the fever is prolonged (Table 32–2).

Other findings consist of conjunctivitis, mild vitritis, retinal lesions, optic neuritis, and hearing loss from neuropathy of the eighth cranial nerve, abdominal pain, and often splenomegaly. Flushed faces and macular rash (that may become confluent) appear; the rash appears first in the axillae and then over the trunk, spreading to the extremities on the fifth or sixth day of illness but sparing the palms of hands and soles of feet. In severely ill patients, the rash becomes hemorrhagic, and hypotension becomes marked. Pneumonia, thromboses, vasculitis with major vessel obstruction and gangrene, circulatory collapse, myocarditis, uremia, and seizure may occur. Improvement begins 13–16 days after onset with a rapid drop of fever and typically a spontaneous recovery.

B. Laboratory Findings

The white blood cell count is variable. Thrombocytopenia, elevated liver enzymes, proteinuria, and hematuria commonly occur. Serum obtained 5–12 days after onset of symptoms usually shows specific antibodies for *R prowazekii* antigens as demonstrated by complement fixation, microagglutination, or immunofluorescence. In primary rickettsial infection, early antibodies are IgM; in recrudescence (Brill-Zinsser disease), early antibodies are predominantly IgG. A PCR test exists, but its availability is limited.

C. Imaging

Radiographs of the chest may show patchy consolidation.

► Differential Diagnosis

The prodromal symptoms and the early febrile stage lack enough specificity to permit diagnosis in nonepidemic situations. The rash is sufficiently distinctive for diagnosis, but it may be absent in up to 50% of cases or may be difficult to observe in dark-skinned persons. A variety of other acute febrile diseases should be considered, including typhoid fever, meningococcemia, and measles.

► Treatment

Treatment consists of doxycycline 100 mg orally twice daily for 7–10 days or for at least 3 days after the fever subsides. A single dose of 200 mg of doxycycline may be effective; however, some patients may relapse. Chloramphenicol is considered less effective than doxycycline, but it is still the drug of choice in pregnancy.

► Prognosis

The prognosis depends greatly on the patient's age and immune status. The mortality rate is 10% in the second and third decades but in the past, it reached 60% in the sixth decade. Brill-Zinsser disease is rarely fatal.

► Prevention

Prevention consists of louse control with insecticides, particularly by applying chemicals to clothing or treating it with heat, and frequent bathing.

A deloused and bathed typhus patient is not infectious. The disease is not transmitted from person to person. Patients are infectious from the lice during the febrile period and perhaps 2–3 days after the fever returns to normal.

No vaccine is available for the prevention of *R prowazekii* infection.

Centers for Disease Control and Prevention (CDC). Typhus Fevers. <https://www.cdc.gov/typhus/healthcare-providers/index.html>

Ulutasdemir N et al. The epidemic typhus and trench fever are risk for public health due to increased migration in southeast of Turkey. *Acta Trop*. 2018;178:115. [PMID: 29126839]

2. Endemic (Murine) Typhus

Rickettsia typhi, a ubiquitous pathogen recognized on all continents, is transmitted from rat to rat through the rat flea (Table 32–3). Serosurveys of animals show high prevalence of antibodies to *R typhi* in opossums, followed by dogs and cats. Humans usually acquire the infection in an urban or suburban setting when bitten by an infected flea. Rare human cases in the developed world occur in travelers, usually to Southeast Asia, Africa, or the Mediterranean area, although other pockets of infection are also known to occur in the Andes and the Yucatán. In the United States, the related *Rickettsia felis* cases (a spotted fever rickettsia,

discussed below) are mainly reported from Texas and southern California.

► Clinical Findings

A. Symptoms and Signs

The presentation is nonspecific, including fever, headache, myalgia, and chills. Relative bradycardia is reported. Maculopapular rash occurs in around 50% of cases; it is concentrated on the trunk, mostly sparing the palms and soles, and fades rapidly.

Even if untreated, endemic typhus is usually self-limited, and the prognosis is excellent. One recent systematic review including 239 untreated patients from 12 studies reported an overall mortality of 0.4%. The illness may be associated with maternal death, miscarriage, preterm birth, and low birth weight if acquired early during pregnancy.

B. Laboratory Findings

Serologic confirmation may be necessary for differentiation, with complement-fixing or immunofluorescent antibodies detectable within 15 days after onset, with specific *R typhi* antigens. A fourfold rise in serum antibody titers between the acute and the convalescent phase is diagnostic. It is important to note that *R typhi* antigens frequently cross-react with those of *R prowazekii*. The PCR can distinguish between these two infections depending on the sample type, the timing of sample collection, bacterial load, and severity of disease. During the first week of illness, PCR is the most sensitive test if samples are taken before doxycycline administration.

► Differential Diagnosis

The most common entity in the differential diagnosis is Rocky Mountain spotted fever, usually occurring after rural exposure and with a different rash (centripetal versus centrifugal for epidemic or endemic typhus).

► Complications

The most common complication is pulmonary, in the form of pneumonia, followed by pleural effusion and respiratory failure. Other complications include neurologic (peripheral facial paralysis, meningismus, ataxia, seizures), acute kidney injury, and multiorgan failure. Rare complications include ocular findings, disseminated intravascular coagulation, and hemophagocytosis syndrome. Anemia, thrombocytopenia, leukopenia, hyponatremia, and elevated levels of liver enzymes commonly occur.

► Treatment

Doxycycline 100 mg orally twice daily for 3 days (or until the patient is afebrile for 48 hours) is the medication of choice, except during pregnancy. Ciprofloxacin (500–750 mg orally twice a day) and ampicillin (500 mg orally three times a day) are reportedly successful in pregnant women. Azithromycin is frequently used but is likely inferior to doxycycline and is not associated with improved fetal outcomes.

Table 32–3. Rickettsial diseases (listed in alphabetical order, within groups).

Disease	Rickettsial Pathogen	Geographic Areas of Prevalence	Insect Vector	Mammalian Reservoir	Travel Association
Typhus Group					
Endemic (murine) typhus	<i>Rickettsia typhi</i>	Worldwide; small foci (United States: southeastern Gulf Coast)	Flea	Rodents, opossums	Often
Epidemic (louse-borne) typhus	<i>Rickettsia prowazekii</i>	South America, Northeastern and Central Africa	Louse	Humans, flying squirrels	Rare
Scrub Typhus Group					
Scrub typhus	<i>Orientia tsutsugamushi</i>	Southeast Asia, Japan, Australia, Western Siberia	Mite ¹	Rodents	Often
Spotted Fever Group					
African tick bite fever	<i>Rickettsia africae</i>	Rural sub-Saharan Africa, Eastern Caribbean	Tick ¹	Cattle	Often
California flea rickettsiosis	<i>Rickettsia felis</i>	Worldwide	Flea	Cats, opossums	
Lymphangitis-associated rickettsiosis	<i>R sibirica mongolitimonae</i>	Europe, Africa, Mongolia	Tick ¹	Unknown	Unknown
Mediterranean spotted fever, Boutonneuse fever, Kenya tick typhus, South African tick fever, Indian tick typhus	<i>Rickettsia conorii</i>	Africa, India, Mediterranean regions	Tick ¹	Rodents, dogs	Often
Queensland tick typhus	<i>Rickettsia australis</i>	Eastern Australia	Tick ¹	Rodents, marsupials	Rare
Rocky Mountain spotted fever, Brazilian spotted fever	<i>Rickettsia rickettsii</i>	Western Hemisphere; United States (especially mid-Atlantic coast region) Southeastern Brazil	Tick ¹	Rodents, dogs, porcupines, capybaras for Brazilian spotted fever	Rare
Siberian Asian tick typhus	<i>Rickettsia sibirica</i>	Siberia, Mongolia	Tick ¹	Rodents	Rare
Tick-borne lymphadenopathy/ <i>Dermacentor</i> -borne necrosis erythema lymphadenopathy/scalp eschar neck lymphadenopathy	<i>R slovaca</i> , <i>R raoultii</i> , <i>Candidatus R riolettaiae</i>	Europe	Tick	Unknown	Occasional
Transitional Group					
Rickettsialpox	<i>Rickettsia akari</i>	United States, Korea, former USSR	Mite ¹	Mice	Occasional
Ehrlichiosis/Anaplasmosis					
Human granulocytic anaplasmosis	<i>Anaplasma phagocytophilum</i> , <i>Ehrlichia ewingii</i> , <i>Ehrlichia muris eauclairensis</i> ² <i>Neorickettsia sennetsu</i> ²	Northeastern United States and upper Midwest (<i>E muris eauclairensis</i>) Southeast Asia (<i>N sennetsu</i>)	Tick ¹	Rodents, deer, sheep	Occasional
Human monocytic ehrlichiosis	<i>Ehrlichia chaffeensis</i> , <i>Ehrlichia canis</i>	Southeastern United States	Tick ¹	Dogs	Occasional
Q fever	<i>Coxiella burnetii</i>	Worldwide	None ³	Cattle, sheep, goats	Occasional

¹Also serve as arthropod reservoirs by maintaining rickettsiae through transovarian transmission.²Limited data available on exact cell involved in pathogenesis.³Human infection results from inhalation of dust.

► Prevention

Preventive measures are directed at control of rats and ectoparasites (rat fleas) with insecticides, rat poisons, and rat-proofing of buildings.

► Prognosis

Endemic typhus is usually a self-limited disease. A large case series from Texas reported a fatality rate of 0.4%.

Doppler JF et al. A systematic review of the untreated mortality of murine typhus. *PLoS Negl Trop Dis.* 2020;14:e0008641. [PMID: 32925913]

Newton PN et al. A prospective, open-label, randomized trial of doxycycline versus azithromycin for the treatment of uncomplicated murine typhus. *Clin Infect Dis.* 2019;68:738. [PMID: 30020447]

3. Scrub Typhus (Tsutsugamushi Fever)



ESSENTIALS OF DIAGNOSIS

- ▶ Exposure to mites in endemic South and East Asia, the western Pacific (including Korea), and Australia.
- ▶ Black eschar at site of the bite, with regional and generalized lymphadenopathy.
- ▶ High fever, relative bradycardia, headache, myalgia, and a short-lived macular rash.
- ▶ Frequent pneumonitis, encephalitis, and myocarditis.

► General Considerations

Scrub typhus is caused by *Orientia tsutsugamushi*, which is a parasite of rodents and is transmitted by larval trombiculid mites (chiggers). Multiple strains exist and are associated with geographic areas. The disease is endemic in Korea; China; Taiwan; Japan; Pakistan; India (where it is reported to be the leading cause of acute febrile illness in central India); Thailand (where scrub typhus is also the leading cause of acute undifferentiated fever); Malaysia; Vietnam; Laos; and Queensland, Australia (Table 32–3), which form an area known as the “tsutsugamushi triangle.” Scrub typhus is a cause of acute febrile illness in India and China and is a recognized cause of fever of unknown origin. Cases are also reported in the Middle East, Kenya, and South America. Transmission is often more common at higher altitudes. The mites live on vegetation (grass and brush) but complete their maturation cycle by biting humans who encounter infested vegetation. Risk factors in China include female sex, age between 60 and 69 years, and farming. Therefore, the disease is more common in rural areas, but urban cases have also been described. Vertical transmission occurs, and blood transfusions may transmit the pathogen as well. Rare occupational transmission via inhalation is documented among laboratory workers. Cases among travelers to endemic areas are increasingly recognized.

► Clinical Findings

A. Symptoms and Signs

After a 1- to 3-week incubation period, malaise, chills, severe headache, and backache develop. At the site of the bite, a papule evolves into a flat black eschar (the groin and the abdomen being the most common sites followed by the chest and axilla), which is a helpful finding for diagnosis but was only described in 19% of patients in a South Korean series of scrub typhus. The regional lymph nodes are commonly enlarged and tender, and sometimes a more generalized adenopathy occurs. Fever rises gradually during the first week of infection, and the rash is usually macular and primarily on the trunk area. The rash can be fleeting or more severe, peaking at 8 days but lasting up to 21 days after onset of infection. Relative bradycardia, defined as an increase in heart rate of fewer than 10 beats/min for a 1-degree Celsius increase in temperature, frequently accompanies scrub typhus infection. The occurrence of relative bradycardia has no effect on clinical outcome. Gastrointestinal symptoms, including nausea, vomiting, and diarrhea, occur in nearly two-thirds of patients and correspond to the presence of superficial mucosal hemorrhage, multiple erosions, or ulcers in the gastrointestinal tract. Acute kidney injury and other renal abnormalities are frequently present.

Severe complications, such as pneumonitis, myocarditis, encephalitis or aseptic meningitis, peritonitis, granulomatous hepatitis, hemophagocytic syndrome, immune thrombocytopenia, disseminated intravascular coagulation, cerebrovascular hemorrhage or infarction, cranial nerve palsies, parkinsonian symptoms, ARDS, or hemophagocytosis, may develop during the second or third week. An attack confers prolonged immunity against homologous strains and transient immunity against heterologous strains. Heterologous strains produce mild disease if infection occurs within a year after the first episode.

B. Laboratory Findings

Thrombocytopenia and elevation of liver enzymes, bilirubin, and creatinine are common. Indirect immunofluorescent assay and indirect immunoperoxidase assays are the gold standard for scrub typhus diagnosis. These tests are expensive and have limited availability. An ELISA detecting *Orientia* specific antibodies in serum is available. PCR (from the eschar or blood) is the most sensitive diagnostic test but remains positive even after initiation of treatment. Culture of the organism from blood obtained in the first few days of illness is another diagnostic modality but requires a specialized BSL 3 laboratory. It is suggested to combine IgM detection by ELISA and conventional PCR to improve the diagnosis of scrub typhus.

► Differential Diagnosis

Leptospirosis, typhoid, dengue, malaria, Q fever, hemorrhagic fevers, tuberculous meningitis, and other rickettsial infections should be considered. The headache may mimic trigeminal neuralgia. Scrub typhus is a recognized cause of obscure tropical fevers, especially in children. The presence

of an eschar, lymphocytosis, and elevated C-reactive protein (CRP) may help distinguish scrub typhus from dengue.

Treatment & Prognosis

Without treatment, fever subsides spontaneously after 2 weeks, but the mortality rate may be 10–30%. The treatment of choice is doxycycline (100 mg orally twice daily) or minocycline (100 mg intravenously twice daily) until there is evidence of clinical improvement for at least 3 days after the fever subsides. Shorter duration of therapy is associated with relapse. A 2018 randomized controlled trial comparing doxycycline to rifampin showed that 600 mg of rifampin daily for 5 days is noninferior to 200 mg of daily doxycycline therapy for 5 days. Alternative therapy for pregnant women and patients with doxycycline allergy include chloramphenicol, although chloramphenicol- and tetracycline-resistant strains have been reported from Southeast Asia. Azithromycin is shown to be as effective as doxycycline with fewer side effects, but it is more expensive. Azithromycin may not prevent poor fetal outcomes in infected pregnant women.

Poor prognostic factors include hypotension requiring vasopressors, ICU care, age over 60 years, absence of an eschar (making the diagnosis difficult), pregnancy, and laboratory findings such as leukocytosis or hypoalbuminemia. Most patients recover without neurologic sequelae.

Prevention

Mite control with repeated application of long-acting miticides and, less so, rodent control can make endemic areas safe. Insect repellents on clothing and skin as well as protective clothing are effective preventive measures. Although chemoprophylaxis with doxycycline has been used, the CDC does not recommend prophylaxis with antibiotics for asymptomatic travelers. No effective vaccines are available.

Kim YS et al. Effects of rifampin and doxycycline treatments in patients with uncomplicated scrub typhus: an open-label, randomized, controlled trial. *Clin Infect Dis*. 2018;67:600. [PMID: 29462266]

Richards AL et al. Scrub typhus: historic perspective and current status of the worldwide presence of *Orientia* species. *Trop Med Infect Dis*. 2020;5:49. [PMID: 32244598]

Wangrangsimakul T et al. Scrub typhus and the misconception of doxycycline resistance. *Clin Infect Dis*. 2020;70:2444. [PMID: 31570937]

- ▶ Red macular rash appears between days 2 and 6 of fever, first on the wrists and ankles and then spreading centrally; it may become petechial.
- ▶ Mortality over 70% in untreated patients.
- ▶ Serial serologic examinations by indirect fluorescent antibody confirm the diagnosis retrospectively.

General Considerations

Rocky Mountain spotted fever (RMSF) is caused by *Rickettsia rickettsii* and is endemic in parts of the Americas (Table 32–3). In the United States, the numbers of RMSF cases have increased over the last two decades, peaking in 2017 at 6248. Despite its name, most cases of RMSF occur outside the Rocky Mountain area. More than half of US cases are from five states: North Carolina, Tennessee, Oklahoma, Missouri, and Arkansas. Human cases reemerged in northern Mexico in 2008 after decades of quiescence (since the 1940s). As of 2018, northern Mexico reported nearly 4000 RMSF cases.

Rickettsia rickettsii is transmitted to humans by the bite of ticks. Several hours of contact between the tick and the human host are required for transmission. Ticks that can transmit the infection include the Rocky Mountain wood tick, *Dermacentor andersoni*, in the western United States, and the American dog tick, *D. variabilis*, in the eastern United States. Other hard-bodied ticks transmit the organism in the southern United States and in Central and South America and are responsible for transmitting it among rodents, dogs, porcupines, and other animals. The brown dog tick, *Rhipicephalus sanguineus*, is a vector in eastern Arizona and responsible for many Native American cases. Epidemic RMSF, as described in Arizona and Mexico, is associated with massive local infestations of the brown dog tick in domestic dogs, which may explain why the incidence of RMSF in the three most highly affected communities in an Arizona epidemic from 2003 to 2012 was 150 times the US national average.

There are 25 genotypes of *Rickettsia rickettsii* in four different groups, and potential genomic-clinical correlations are underway. Several other rickettsial species cause mild, nonlethal infections in the United States, including *R. parkeri*, *R. phillipi*, and *R. massiliae*. These are discussed in the “tick typhus” section.

A **Brazilian spotted fever** with higher mortality than RMSF is thought to be due to a virulent strain of *Rickettsia rickettsii*. A host of spotted fever species have been identified from human patients over the last 20 years throughout the world including species from China (*Rickettsia* sp. XY99), Slovakia (*R. slovaca*), Morocco (*R. aeschlimannii*), Sicily (*R. massiliiae*), China, and Egypt (*R. sibirica monolitomiae*). Capybaras are a highly mobile vector for the Brazilian disease.

Clinical Findings

A. Symptoms and Signs

RMSF can cause severe multiorgan dysfunction and fatality rates of up to 73% if left untreated, making it the most

SPOTTED FEVERS

1. Rocky Mountain Spotted Fever



ESSENTIALS OF DIAGNOSIS

- ▶ Exposure to tick bite in an endemic area.
- ▶ Influenza-like prodrome followed by fever, severe headache, and myalgias; occasionally, delirium and coma.

Clinical Findings

A. Symptoms and Signs

RMSF can cause severe multiorgan dysfunction and fatality rates of up to 73% if left untreated, making it the most



▲ **Figure 32–8.** Hard palate lesion caused by Rocky Mountain spotted fever. (Public Health Image Library, CDC.)

serious rickettsial disease. Two to 14 days (mean, 7 days) after the bite of an infectious tick, symptoms begin with the abrupt onset of high fever, chills, headache, nausea and vomiting, myalgias, restlessness, insomnia, and irritability. The characteristic rash (faint macules that progress to maculopapules and then petechiae) appears between days 2 and 6 of fever. It initially involves the wrists and ankles, spreading *centrally* to the arms, legs, and trunk over the next 2–3 days. Involvement of the palms and soles is characteristic. Eschars are not usually seen and are more suggestive of rickettsial fevers. Facial flushing, conjunctival injection, and hard palate lesions (Figure 32–8) may occur. In about 10% of cases, however, no rash or only a minimal rash is seen. Cough and pneumonitis may develop, and delirium, lethargy, seizures, stupor, and coma may also appear in more severe cases. Splenomegaly, hepatomegaly, jaundice, myocarditis (which may mimic an acute coronary syndrome), adrenal hemorrhage, polyarticular arthritis, or uremia is occasionally present. ARDS and necrotizing vasculitis, when present, are of greatest concern.

In Sonora, Mexico, during 2015–2016, spontaneous abortions were reported in three of four pregnant women with RMSF.

B. Laboratory Findings

Thrombocytopenia, hyponatremia, elevated aminotransferases, and hyperbilirubinemia are common. CSF may show hypoglycorrachia and mild pleocytosis. Disseminated intravascular coagulation is observed in severe cases. Diagnosis during the acute phase of the illness can be made by immunohistologic or PCR demonstration of *R rickettsii* in skin biopsy specimens (or cutaneous swabs of skin lesions). Performing such studies as soon as skin lesions become apparent and before antibiotics commence maximizes sensitivity.

Serologic studies confirm the diagnosis, but most patients do not mount an antibody response until the second week of illness. The indirect fluorescent antibody IgG test is most commonly used.

Diagnosis is most commonly made serologically and 99% of cases are diagnosed with probable disease. It is important that paired sera (acute and convalescent) be used when possible to establish an acute infection.

► Differential Diagnosis

The diagnosis is challenging because early symptoms resemble those of many other infections. The classic triad of fever, rash, and tick bite is rarely recognized, with up to 40% of patients not recalling a tick bite. Moreover, the rash may be confused with that of measles, typhoid, and ehrlichiosis, or—most importantly—meningococcemia. Blood cultures and examination of CSF establish the latter. Coinfections may mask the diagnosis. Some spotted fever rickettsioses may also mimic RMSF but will not be detected by routine serologic testing for RMSF.

► Treatment & Prognosis

Treatment with doxycycline (100 mg orally twice daily for 5–7 days or for at least 3 days after the fever subsides) is recommended in all ages and in pregnant women. Although recent data suggest that doxycycline is unlikely to be a teratogen, pregnant women should be counselled regarding potential risks. Chloramphenicol (50–100 mg/kg/day in four divided doses, orally or intravenously for 4–10 days) is the only alternative medication to treat RMSF; however, patients who are treated with chloramphenicol may be at higher risk for death than people treated with a tetracycline. Note that oral formulations of chloramphenicol are not available in the United States and that use of chloramphenicol potentially has adverse risks such as aplastic anaemia. Patients usually defervesce within 48–72 hours, and therapy should be continued for at least 3 days after defervescence occurs.

The reported mortality rate for treated patients in the United States is about 3–5%. The following features are associated with increased mortality: (1) infection in older adults or Native Americans; (2) the presence of atypical clinical features (absence of headache, no history of tick attachment, gastrointestinal symptoms) and underlying chronic diseases; and (3) a delay in initiation of appropriate antibiotic therapy. The usual cause of death is pneumonitis with respiratory or cardiac failure. A fulminant form of RMSF can be seen in patients with glucose-6-phosphate dehydrogenase deficiency. Sequelae may include seizures, encephalopathy, peripheral neuropathy, paraparesis, bowel and bladder incontinence, cerebellar and vestibular dysfunction, hearing loss, and motor deficits; these sequelae are reported to last for years after the initial infection.

► Prevention

Protective clothing, tick-repellent chemicals, and the removal of ticks at frequent intervals are helpful measures. The effectiveness of aggressive campaigns to decrease ticks in the community is under investigation in communities with high RMSF attack rates. Prophylactic therapy after a tick bite is not recommended.

Binder AM et al. Diagnostic methods used to classify confirmed and probable cases of spotted fever rickettsioses—United States, 2010–2015. MMWR Morb Mortal Wkly Rep. 2019;68:243. [PMID: 30870409]

Erickson T et al. Evidence of locally acquired spotted fever group rickettsioses in Southeast Texas, 2008–2016. Zoonoses Public Health. 2018;65:897. [PMID: 30152119]

2. Tick Typhus (Rickettsial Fever)

The term “tick typhus” denotes a variety of spotted rickettsial fevers, often named by their geographic location (eg, Mediterranean spotted fever, Queensland tick typhus, Oriental spotted fever, African tick bite fever, Siberian tick typhus, North Asian tick typhus) or by morphology (eg, boutonneuse fever). More than 30 species of spotted fever group rickettsioses are found worldwide (mostly in Europe and Asia), 21 of which are pathogenic in humans (including *R rickettsii*, described above). These illnesses are caused by various rickettsial organisms (eg, *R africae*, *R australis*, *R conorii*, *R japonica*, *R massiliae*, *R parkeri*, *R sibirica*, and *R 364D*) and are transmitted by various tick species. Dogs and wild animals, usually rodents and even reptiles, may serve as reservoirs for rickettsial fevers. Travel is a risk factor for disease, particularly among elderly ecotourists. In a series of 280 international travelers with rickettsial disease, the most common cause was spotted fever rickettsiosis (231 cases, 82.5% of the total) followed by scrub typhus (16, 5.7%).

Tick-borne rickettsioses are the main source of rickettsial infections in Europe and cause a syndrome similar to that seen in Mediterranean spotted fever. Physicians from Algeria and India report endemic tick typhus, suggesting a pandemicity of tick-borne rickettsioses. Newer recognized species include *R helvetica*, *R monacensis*, *R massiliae*, and *R aeschlimannii*. Another described syndrome is tick-borne lymphadenopathy/*Dermacentor*-borne-necrosis-erythema-lymphadenopathy/scalp eschar neck lymphadenopathy associated with *R slovaca*, *R candidatus*, *R rioja*, and *R raoultii* and characterized by tick bite, eschar on the scalp, and cervical lymphadenopathy.

The pathogens usually produce an eschar or black spot (tâche noire) at the site of the tick bite that may be useful in diagnosis, though spotless boutonneuse fever occurs. Symptoms include fever, headache, myalgias, and rash. Painful lymphadenopathy or lymphangitis may also occur. Rarely, papulovesicular lesions may resemble rickettsialpox. Endothelial injury produces perivasculär edema and dermal necrosis. Regional adenopathy, disseminated lesions, kidney disease, splenic rupture, and focal hepatic necrosis are observed. A multifocal retinitis is a reported complication. Neurologic manifestations, including encephalitis, internuclear ophthalmoplegia, coronary involvement, and the hemophagocytic syndrome, are rare.

The diagnosis is clinical, with serologic or PCR (culture can be used but is less sensitive than either) of the buffy coat of blood, or an eschar if one is available, used for confirmation. Treatment should be started upon clinical suspicion since delayed therapy is the usual cause of increased morbidity. Oral treatment with doxycycline (100 mg twice daily) or chloramphenicol (50–75 mg/kg/day in four

divided doses) for 7–10 days is indicated. Caution is advised with the use of ciprofloxacin because it is associated with a poor outcome and increases the severity of disease in Mediterranean spotted fever. Primary care practitioners in endemic areas often include macrolides in the management of acute febrile illnesses to cover for these rickettsial fevers. The combination of azithromycin and rifampin is effective and safe in pregnancy. Prevention entails protective clothing, repellents, and inspection for and removal of ticks.

Formerly classified as an endemic or murine typhus, the cat-flea typhus, caused by *R felis* is more properly classified as a spotted fever. The causative agent has been linked to the cat flea and opossum exposure. While the diseases appear to be ubiquitous, most cases in the United States (southern Texas, California, and possibly Hawaii) occur in the spring and summer. Treatment is the same as for other rickettsial fevers.

Cases of non-rickettsiae-associated spotted fever tend to have a better prognosis than those due to *R rickettsiae* infection. Treatment for non-rickettsiae-associated spotted fever as well as *R rickettsiae* infection is with a tetracycline, typically doxycycline, and there is some laboratory evidence that these organisms may be less responsive to macrolides.

Satjanadumrong J et al. Distribution and ecological drivers of spotted fever group rickettsia in Asia. Ecohealth. 2019;16:611. [PMID: 30993545]

3. Rickettsialpox

Rickettsialpox is an acute, self-limiting, febrile illness caused by *Rickettsia akari*, a parasite of mice, transmitted by the mite *Liponyssoides sanguineus* (Table 32–3). Rickettsialpox is in the spotted fever group of rickettsia. *R akari* infections are reported globally. Seroprevalence studies among injection drug users in Baltimore show seropositivity as high as 16%. In New York, its association with poverty is very strong. The illness has also been found in farming communities. Crowded conditions and mouse-infested housing allow transmission of the pathogen to humans. The classic triad of fever, rash, and eschar is found in 99% of cases. The primary lesion is a painless red papule that appears at variable times but on the average a week after a mite bite. The lesion often vesiculates and forms a black eschar.

The onset of symptoms—chills, fever, headache, photophobia, and disseminated aches and pains—is sudden. The fever may be followed by a widespread papular eruption 2–4 days later, with an average of 30–40 lesions that spare the palms and soles. The interval from vesiculation to crust formation is about 10 days. Early lesions may resemble those of chickenpox (typically vesicular versus papulovesicular in rickettsialpox). Pathologic findings include dermal edema, subepidermal vesicles, and at times a lymphocytic vasculitis.

Transient leukopenia and thrombocytopenia and acute hepatitis can occur. A fourfold rise in serum antibody titers to rickettsial antigen, detected by complement fixation or

indirect fluorescent assays, is diagnostic and available through the CDC. Conjugated anti-rickettsial globulin can identify antigen in punch biopsies of skin lesions. PCR detection of rickettsial DNA in fresh tissue also appears of value. *R akari* can also be isolated from eschar biopsy specimens.

Treatment consists of oral doxycycline (200 mg loading dose followed by 100 mg twice daily) for 2–5 days or until defervescence. The disease is usually mild and self-limited without treatment, but occasionally, severe symptoms may require hospitalization. Control requires the elimination of mice from human habitations and insecticide applications.

Vyas NS et al. Investigating the histopathological findings and immunolocalization of rickettsialpox infection in skin biopsies: a case series and review of the literature. *J Cutan Pathol.* 2020;47:451. [PMID: 31955452]

OTHER RICKETTSIAL & RICKETTSIAL-LIKE DISEASES

1. Ehrlichiosis & Anaplasmosis



ESSENTIALS OF DIAGNOSIS

- ▶ Infection of monocyte or granulocyte by tick-borne gram-negative bacteria.
- ▶ Nine-day incubation period; clinical disease ranges from asymptomatic to life-threatening.
- ▶ Malaise, nausea, fever, and headaches.
- ▶ US cases of ehrlichiosis typically occur in men aged 60–69 years; US cases of anaplasmosis typically occur in men aged over 40 years; both occur in the summer, with different geographic areas of prevalence.
- ▶ Excellent response to therapy with tetracyclines.

► General Considerations

Human ehrlichiosis and anaplasmosis are endemic in the United States.

Ehrlichia chaffeensis (Table 32–3), the most common *Ehrlichia* species infecting humans, is seen primarily in the south-central United States (especially Arkansas, Missouri, and Oklahoma). *Ehrlichia ewingii* causes human granulocytic ehrlichiosis similar to anaplasmosis and constitutes almost 10% of ehrlichiosis cases; most cases in the United States are reported from the Midwest and Southeast. Human granulocytic anaplasmosis is caused by *Anaplasma phagocytophilum*; most cases in the United States are reported from New England, New York, Minnesota, and Wisconsin. Increasingly, anaplasmosis is being reported from Asia, South Korea, Mongolia, China (where a new species is identified, *Anaplasma capra*), and Northern Europe.

In North America, the major tick-borne rickettsial disease vectors for these pathogens are (1) the Lone Star tick (*Amblyomma americanus*), which is the vector for

E chaffeensis and *E ewingii*; (2) the black-legged tick (*Ixodes scapularis*), which is a vector for *B burgdorferi* (Lyme disease), *Babesia microti* (babesiosis), and *A phagocytophilum* (anaplasmosis), and a possible vector for *Ehrlichia muris eauclairensis*; and (3) the western black-legged tick (*Ixodes pacificus*), which is a vector for *A phagocytophilum* along the Pacific coast of the United States. Vectors for European and Asian cases are not reported to date. The principal reservoirs for human monocytic ehrlichiosis and human granulocytic anaplasmosis are the white tail deer and the white-footed mouse, respectively. Other mammals are implicated as well. Transfusion-transmitted anaplasmosis has been reported.

CDC reports indicate that the incidences of human monocytic ehrlichiosis, granulocytic ehrlichiosis and, in particular, anaplasmosis are increasing; cases are reportable to local and state health departments. Because more than one agent may coexist in the same area, cases of human ehrlichiosis and anaplasmosis may be reported as “human ehrlichiosis/anaplasmosis undetermined” in the absence of species identification.

The case fatality rate is 1% with *E chaffeensis* infections and 0.3% among cases of human anaplasmosis. Most cases of *E ewingii* infection have occurred among immunocompetent patients. No deaths have been reported from either *E ewingii* or *E muris eauclairensis*.

► Clinical Findings

A. Symptoms and Signs

Clinical disease of human monocytic ehrlichiosis ranges from mild to life-threatening. Typically, after a 1- to 2-week incubation period and a prodrome consisting of malaise, rigors, and nausea, high fever and headache develop. A pleomorphic rash may occur. Presentation in immunosuppressed patients (including transplant patients) and older patients tends to be more severe. Rare serious sequelae include acute respiratory failure and ARDS; neurologic complications, the most common being meningoencephalitis and aseptic meningitis; acute kidney disease (which may mimic thrombotic thrombocytopenic purpura); hemophagocytic syndrome; and multiorgan failure.

The clinical manifestations of human granulocytic ehrlichiosis and anaplasmosis are similar to those seen with human monocytic ehrlichiosis. Rash, however, is infrequent. If a rash is present, coinfection with other tick-borne diseases or an alternative diagnosis should be suspected. Persistent fever and malaise are reported to occur for 2 or more years. Reported complications of anaplasmosis include leukopenia, thrombocytopenia, and cerebral infarction.

Coinfection with anaplasmosis and Lyme disease or babesiosis may occur, but the clinical manifestations (including fever and cytopenias) are more severe with anaplasmosis than with Lyme disease. A spirochete, *Borrelia miyamotoi*, may mimic anaplasmosis in its clinical manifestations.

B. Laboratory Findings

Diagnosis can be made by the history of tick exposure followed by a characteristic clinical presentation. Leukopenia, absolute lymphopenia, thrombocytopenia, and

transaminitis occur often. Thrombocytopenia occurs more often than leukopenia in human granulocytic ehrlichiosis. Examination of peripheral blood with Giemsa stain may reveal characteristic intraleukocytic vacuoles (morulae) in up to 20% of patients. An indirect fluorescent antibody assay is available through the CDC and requires acute and convalescent sera. A PCR assay can be helpful for making the diagnosis early in the disease course. PCR assay is most sensitive in the first week of illness and can be used as a confirmatory test.

Treatment & Prevention

Treatment for human ehrlichiosis and anaplasmosis is with doxycycline, 100 mg twice daily (orally or intravenously) for 10–14 days or until 3 days of defervescence. Rifampin is an alternative in pregnant women. Treatment should not be withheld while awaiting confirmatory serology when suspicion is high. Lack of clinical improvement and defervescence 48 hours after doxycycline initiation suggests an alternate diagnosis. Some patients may continue to have headache, weakness, and malaise for weeks despite adequate treatment. Tick control is the essence of prevention.

Centers for Disease Control and Prevention (CDC). Ehrlichiosis: epidemiology and statistics. <https://www.cdc.gov/ehrlichiosis/stats/index.html>

Centers for Disease Control and Prevention (CDC). Anaplasmosis: epidemiology and statistics. <https://www.cdc.gov/anaplasmosis/stats/index.html>

2. Q Fever (*Coxiella burnetii* Infection)



ESSENTIALS OF DIAGNOSIS

- ▶ Exposure to sheep, goats, cattle, or their products; some infections are laboratory acquired.
- ▶ Acute or chronic febrile illness: headache, cough, prostration, and abdominal pain.
- ▶ Pneumonitis, hepatitis, or encephalopathy; less often, endocarditis, vascular infections, or chronic fatigue syndrome.
- ▶ A common cause of culture-negative endocarditis.

General Considerations

Q fever, a reportable and significantly underestimated disease in the United States, is caused by the gram-negative intracellular coccobacillus *C. burnetii*. *Coxiella* infections occur globally, mostly in cattle, sheep, and goats, in which they cause mild or subclinical disease (Table 32–3). In these animals, reactivation of the infection occurs during pregnancy and causes abortions or low birth weight offspring. *Coxiella* is resistant to heat and drying and remains infective in the environment for months.

Human infection occurs via inhalation of aerosolized bacteria (in dust or droplets) from feces, urine, milk, or products of conception of infected animals. Ingestion and

skin penetration are other recognized routes of transmission. A 2017 outbreak in Spain had an attack rate of 25% (16/64). There is a known occupational risk for animal handlers, slaughterhouse workers, veterinarians, laboratory workers, and other workers exposed to animal products. In the United States, over 60% of cases do not report an exposure to potentially infectious animals, but cases are more than twice as likely as non-cases to report drinking raw milk.

Human-to-human transmission does not seem to occur, but maternal-fetal infection can occur and infection after liver transplant is reported.

Clinical Findings

A. Symptoms and Signs

Asymptomatic infection is common. For the remaining cases, a febrile illness develops after an incubation period of 2–3 weeks, usually accompanied by headache, relative bradycardia, prostration, and muscle pains. The clinical course may be acute, chronic (duration 6 months or longer), or relapsing. Pneumonia and granulomatous hepatitis are the predominant manifestations in the acute form (and these may vary in incidence geographically), whereas other less common manifestations include skin rashes (maculopapular or purpuric), fever of unknown origin, myocarditis, pericarditis, aortic aneurysms, aseptic meningitis, encephalitis, orchitis, iliopsoas abscess, spondylodiscitis, tenosynovitis, granulomatous osteomyelitis (more often seen in children), and regional (mediastinal) or diffuse lymphadenopathies.

It has been recommended that the term “chronic Q fever” be abandoned to avoid confusion and be replaced with “persistent localized infections.” The most common presentation in patients with persistent localized infections is culture-negative endocarditis. Risk factors for endocarditis are the immunocompromised state, presence of preexisting valvular conditions, male sex, and age above 40 years. Valvular prosthesis (mechanical or bioprostheses) represents the most important risk factor. In series of post-cardiac surgery patients with culture-negative endocarditis, Q fever is the most common cause (about 40% of cases).

The clinical manifestations of endocarditis are nonspecific with fever, night sweats, and weight loss. Rarely, urticaria, edema, erythema nodosum, and arthralgias are reported. Sudden cardiac insufficiency, stroke, or other embolic and mycotic aneurysms can also develop. Vascular infections, particularly of the aorta (causing mycotic aneurysms) and of graft prostheses, are the second most common presentation and are associated with a high mortality (25%). A post-Q fever chronic fatigue syndrome (1 year after acute infection with chronic symptoms) is controversial and of unknown pathophysiology. Cognitive behavioral therapy is effective in reducing fatigue severity in patients with Q fever fatigue syndrome; long-term treatment with doxycycline has not been shown to be effective.

New infection or reactivation of Q fever can occur in pregnant women and is associated with spontaneous abortions, intrauterine growth retardation, intrauterine fetal

death, and premature delivery. *C. burnetii* infection during the first trimester can cause oligohydramnios.

B. Laboratory Findings

Laboratory examination during the acute phase may show elevated liver biochemical tests and occasional leukocytosis. Patients with acute Q fever usually produce antibodies to *C. burnetii* phase II antigen (phase II antigens are formed in vitro from deleted avirulent mutants and are empirically more commonly seen in acute disease, whereas phase I antigens, seen in nature and laboratory infections, are found in the IgG form in chronic disease). A fourfold rise between acute and convalescent sera by indirect immunofluorescence is diagnostic of the infection. Real-time PCR for *C. burnetii* DNA is helpful only in early diagnosis of Q fever. *C. burnetii* DNA becomes undetectable in serum as serologic responses develop. The positive predictive value of antibodies to phase II antigens in acute disease is at most 65%, and considerable intertest variability exists with phase 2 antigens. Diagnostic tests combining PCR with ELISA (Immuno-PCR) improve the sensitivity and specificity during the first 2 weeks after the onset of symptoms.

While persistent infection can be diagnosed based on serologic tests done at 3- and 6-month intervals (with an IgG titer against phase I antigen of 1:800 or greater), the sensitivity of such serologies is often low, and the diagnosis of Q fever is often made clinically. An automated epifluorescence assay has greater than 95% sensitivity for the detection of phase I antigens in persistent infection. The presence of elevated levels of anticardiolipin antibodies have a high positive predictive value for acute endocarditis.

Diagnosis of Q fever endocarditis is often made at the time of valve replacement with PCR of tissue samples. *C. burnetii* may also be isolated from affected valves using the shell-vial technique.

C. Imaging

Radiographs of the chest can show patchy pulmonary infiltrates. All patients with acute Q fever should be screened for underlying valvular disease with echocardiography. Initial imaging and follow-up with serial 18-FDG PET/CT scan may be helpful in identifying chronic infection and monitoring treatment response.

Differential Diagnosis

Viral, *Mycoplasma*, and bacterial pneumonias; viral hepatitis; brucellosis; Legionnaire disease; murine or scrub typhus; Kawasaki disease; tuberculosis; psittacosis; and other animal-borne diseases can have similar clinical presentations to Q fever. Q fever should be considered in cases of unexplained fevers with negative blood cultures in association with embolic or cardiac disease. Cases of Q fever can mimic autoimmune disease. Coinfection with typhus and leptospirosis is reported.

Treatment & Prognosis

Doxycycline is the most effective medication against *C. burnetii*; there are rare reports of doxycycline resistance.

Isolates remain susceptible to levofloxacin, moxifloxacin, and to a lesser extent ciprofloxacin. No resistance to sulfamethoxazole-trimethoprim is reported to date.

For acute infection, treatment with doxycycline (100 mg orally twice daily) for 14 days or at least 3 full days after defervescence is recommended. Even in untreated patients, the mortality rate is usually low, except when endocarditis develops.

There are no consensus guidelines on the treatment of persistent *C. burnetii* infections. Most experts recommend a combination oral therapy with doxycycline (100 mg twice a day) plus hydroxychloroquine for approximately 18 months for native valve endocarditis and 24 months for prosthetic valve endocarditis. The use of alternative combination regimens with a quinolone or rifampin shows some efficacy.

Serologic responses can be monitored during and after completion of therapy and treatment can be extended in the absence of favorable serologic response. The general variability of serologic data, however, limits their usefulness and providers usually rely on clinical criteria. Patients should be monitored for an extended period of time, generally at least several years per expert opinion, due to risk of relapse.

For patients with endocarditis, clinical cure is possible without valve replacement. Heart valve replacement is not associated with better survival, except in the group of patients with a valvular prosthesis. Given the difficulty in treating endocarditis, transthoracic echocardiography is recommended to screen for predisposing valvulopathy in all patients with acute Q fever, and the same therapy for 1 year should be offered in the presence of valvulopathy. In addition, patients undergoing routine valve surgery in endemic countries should be evaluated via Q fever serology and treated if positive.

All infected pregnant women should be given long-term trimethoprim-sulfamethoxazole (320/1600 mg orally for the duration of pregnancy, but not beyond 32 weeks' gestation) to prevent the obstetric complications.

In retrospective studies, an increased risk of diffuse B-cell lymphoma and follicular lymphoma was found in patients with Q fever compared with the general population. Patients with persistent focalized infections were at higher risk for lymphadenitis and progression to lymphoma.

Prevention

Prevention is based on detection of the infection in livestock, with reduction of contact with infected and parturient animals or contaminated dust; special care when working with animal tissues; and effective pasteurization of milk. A whole-cell Q fever vaccine is available in Australia for persons with high-risk exposures, although there are reports of vaccine failure more than 15 days after vaccination.

The organism is highly transmissible to laboratory workers and culture techniques require a biosafety level 3 setting. *C. burnetii* is a category B bioterrorism agent. In the setting of a bioterrorist attack, postexposure prophylaxis with doxycycline 100 mg orally twice a day for 5–7 days should be administered within 8–12 days of exposure. Pregnant women may take trimethoprim-sulfamethoxazole as an alternative.

Centers for Disease Control and Prevention (CDC). National Notifiable Diseases Surveillance System (NNDSS): Q Fever (*Coxiella burnetii*) 2009 Case Definition <https://www.cdc.gov/nndss/conditions/q-fever/case-definition/2009/>
 Mboussou Y et al. Pregnancy outcomes of Q fever: prospective follow-up study on Reunion island. *BMC Infect Dis.* 2019;19: 1001. [PMID: 31775645]

KAWASAKI DISEASE



ESSENTIALS OF DIAGNOSIS

- ▶ Fever, conjunctivitis, oral mucosal changes, rash, cervical lymphadenopathy, peripheral extremity changes.
- ▶ Elevated ESR and CRP levels.
- ▶ Risk for coronary arteritis and aneurysms.

General Considerations

Kawasaki disease is a worldwide multisystem disease. It is also known as the “mucocutaneous lymph node syndrome.” It occurs mainly in children between the ages of 3 months and 5 years but can occur occasionally in adults as well. Kawasaki disease occurs most often in Asians or native Pacific Islanders. Its incidence in Japan is twice that of the United States, and it occurs among siblings at twice the incidence of cases and at higher rates among parents of cases. These findings plus the known seasonality (higher incidence in winter and early spring) and occasional epidemic pattern of cases point to the inadequate current understanding of the etiology of this disease.

Kawasaki disease is an acute, self-limiting, mucocutaneous vasculitis characterized by the infiltration of vessel walls with mononuclear cells and later by IgA secreting plasma cells that can result in the destruction of the tunica media and aneurysm formation. The cause remains unknown. Epidemiologic studies show an increased risk with advanced maternal age, mother of foreign birth, maternal group B *Streptococcus* colonization, and early infancy hospitalization for a bacterial illness. Genetic factors are considered to play an important role in the pathogenesis of the disease. Ongoing analyses identify many gene polymorphisms, which significantly correlate with Kawasaki disease susceptibility (at least 23 to disease, and 10 to the presence of coronary aneurysms).

The Kawasaki-like disease, called **multisystem inflammatory syndrome in children (MIS-C)**, is described in the section above on SARS-CoV-2.

Clinical Findings

A. Symptoms and Signs

A clinical diagnosis of classic or “**complete**” Kawasaki disease requires the presence of at least 5 days of fever, usually high-grade (over 39°C to 40°C) and four of the following five criteria: (1) bilateral nonexudative conjunctivitis

(begins shortly after the onset of fever), (2) oral changes of erythema and cracking of lips, strawberry tongue, and erythema of oral and pharyngeal mucosa (ulcers and pharyngeal exudates are not consistent with Kawasaki disease), (3) peripheral extremity changes (erythema and edema of the hands and feet in the acute phase, and/or periungual desquamation within 2 to 3 weeks after the onset of fever), (4) polymorphous rash, and (5) cervical lymphadenopathy (larger than 1.5 cm, usually unilateral; least common of the clinical features). The revised case definition allows the diagnosis on day 4 in the presence of more than four principal clinical criteria, particularly when redness and swelling of the hands and feet are present.

A diagnosis of atypical or “**incomplete**” Kawasaki disease can be made in patients with unexplained fever and fewer than four principal criteria if accompanied by compatible laboratory tests or findings of aneurysms detected by echocardiography or angiography.

B. Laboratory Findings

Laboratory findings in the acute phase of Kawasaki disease typically include leukocytosis with neutrophilic predominance, anemia, and an elevated ESR and CRP. High platelet counts are characteristic but occur in the second week. N-terminal moiety of B-type natriuretic peptide (NT-proBNP), likely indicative of myocardial involvement, may be elevated in some patients with Kawasaki disease.

The laboratory components of the CDC’s case definition of MIS-C are positivity for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test (or known COVID-19 exposure within the 4 weeks prior to the onset of symptoms) in conjunction with evidence of inflammation (including one or more of the following: elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase, interleukin-6 [IL-6], or neutrophils; or reduced lymphocytes or albumin).

Major complications include arteritis and aneurysms of the coronary vessels. The arteritis begins 6–8 days after the onset of disease, occurs in about 25% of untreated patients, and occasionally causes myocardial infarction. Coronary complications are more common among patients older than 6 years or younger than 1 year of age; males; and those unresponsive to IVIG, who received a smaller dose of IVIG, or did not receive treatment within 10 days of symptom onset. According to the 2017 American Heart Association definitions of coronary artery aneurysm, such aneurysms developed in 6.4% of patients with Kawasaki disease despite treatment with IVIG and aspirin. While myocarditis can be found in all patients with Kawasaki disease on histologic specimens and is prominent during the acute stage, only a small percentage of patients are clinically symptomatic.

Cardiac complications include left ventricular dysfunction, which usually normalizes promptly with IVIG therapy, and mitral regurgitation, which occurs early and does not appear to persist. Noninvasive diagnosis of coronary complications can be made with CT coronary angiography (the most sensitive test), magnetic resonance angiography, or transthoracic echocardiography (advocated for early screening). Kawasaki shock syndrome is a complication,

with an estimated incidence of 7%, possibly caused by decrease in peripheral vascular resistance, myocarditis with or without myocardial ischemia, and capillary leakage.

The multisystemic findings of Kawasaki disease show it to be a systemic disease that affects medium-sized arteries of multiple organs, causing elevations in serum transaminases, interstitial pneumonitis, abdominal pain, vomiting, diarrhea, gallbladder hydrops, pancreatitis, lymphadenopathy, hypoalbuminemia, arrhythmias, aseptic meningitis, acute encephalopathy with biphasic seizures and late reduced diffusion, retinal and choroidal detachment, pulmonary complications (effusions, empyema, pneumothorax), and pyuria. CSF pleocytosis with a mononuclear cell predominance, normal glucose levels, and protein levels is seen in one-third of children who undergo lumbar puncture.

Other diseases with similar presentation that should be considered include measles in unimmunized children as well as other viral infections, such as SARS-CoV-2, adenovirus, scarlet fever, hemophagocytic lymphohistiocytosis syndrome, and toxic shock syndrome; rickettsial infections; or leptospirosis and drug hypersensitivity reactions.

► Treatment & Prevention

All patients meeting the diagnostic criteria for Kawasaki disease (complete and incomplete), including patients with recurrent Kawasaki disease, should be treated as soon as the diagnosis is suspected to reduce inflammation and arterial damage.

A single dose of IVIG should be given in the first 10 days of the illness. Patients in whom the diagnosis was made later than the tenth day may still benefit from IVIG treatment if they have elevated inflammatory markers (ESR or CRP), with persistent fever or have coronary artery aneurysms. When IVIG treatment is not given, coronary artery aneurysms occur in 20% of children. Even when treated with IVIG within the first 10 days of illness, coronary artery aneurysms still develop in 5% of patients. Rare cases of aseptic meningitis are reported with IVIG. Coombs-positive hemolytic anemia, especially in individuals with AB blood type and anaphylactic reactions to immunoglobulins with selective IgA deficiency are other complications associated with IVIG administration.

Although aspirin does not lower the frequency of development of coronary abnormalities, it has important anti-inflammatory activity and antiplatelet activity. Concomitant aspirin with IVIG should be started at 80–100 mg/kg/day orally (divided into four doses and not exceeding 4 g/day) until the patient is afebrile for 48 hours and then reduced to 3–5 mg/kg/day until markers of acute inflammation normalize. A 2019 meta-analysis indicates that low-dose aspirin (3–5 mg/kg/day) may be as effective as the use of high-dose aspirin (30 mg/kg/day or more) for the initial treatment of Kawasaki disease. Since ibuprofen antagonizes the irreversible platelet inhibition induced by aspirin, it should be avoided when aspirin is given.

The use of corticosteroids for children with Kawasaki disease is controversial. According to the 2017 published guidelines by the American Heart Association, single-dose pulse methylprednisolone should not be used routinely for

patients with Kawasaki disease. A course of corticosteroid therapy with tapering over 2–3 weeks could be considered in addition to IVIG and aspirin for patients at high-risk for not responding to IVIG.

Resistant Kawasaki disease, defined as having recrudescent or persistent fever at least 36 hours after the end of the first IVIG infusion when no other source of fever is found, develops in about 10–20% of patients. The Egami score is a predictor used in Japan to help determine who will respond to IVIG, although the scoring system has been shown to have lower utility in US cases. The presence of coronary artery abnormalities on the initial echocardiogram and their presence before day 5 of fever predict non-response to IVIG in one Israeli study.

Options for refractory cases include a second dose of IVIG, high-dose pulse corticosteroids over 3 days with or without a subsequent oral taper course, longer oral tapering course of corticosteroids over 2–3 weeks together with IVIG and aspirin, TNF-alpha blockers such as infliximab, the anti-inflammatory interleukin-1 receptor antagonist anakinra, low-dose methotrexate, and cyclosporine. Immunomodulatory monoclonal antibody therapy and cytotoxic agents or (rarely) plasma exchange should be considered only in highly refractory cases in which other therapy has failed.

The most common serious complication in the acute phase is thrombotic occlusion of a coronary artery aneurysm leading to myocardial infarction or sudden death. An echocardiogram is recommended within 1–2 weeks and 4–6 weeks after treatment for uncomplicated patients. More frequent imaging is recommended for patients with significant and evolving coronary artery abnormalities. Anticoagulation with warfarin or low-molecular-weight heparin is indicated, along with aspirin, in patients with rapidly expanding coronary artery aneurysms. Aspirin, a second antiplatelet agent, and anticoagulation with warfarin, low-molecular-weight heparin, or direct-acting oral anticoagulants (which need further study in this population) may be considered for patients with large or giant aneurysms (at least 8 mm) (which correlate with delay in diagnosis) and a recent history of coronary artery thrombosis. Platelets from Kawasaki patients treated with antiplatelet agents do show decreased platelet aggregation function. Systemic arterial aneurysms are also recognized and always occur concomitantly with coronary aneurysms, and large systemic aneurysms show a high rate of regression.

If myocardial infarction occurs, therapy with thrombolytics, percutaneous coronary intervention, coronary artery bypass grafts, and even cardiac transplantation should be considered. Manifestations of coronary artery aneurysms can occur as late as in the third or fourth decade of life with a study showing a prevalence of 5% coronary sequelae from Kawasaki disease among young adults evaluated with angiography. Calcified coronary aneurysms on CT scans are less likely to regress.

► Prognosis

The reported recurrence rate is 3% in one study from Japan. The highest risk of recurrence occurs in the first 2 years after the first episode. The mortality peaks between

15 and 45 days after the onset of fever, at the time of coronary artery vasculitis, thrombocytosis, and a hypercoagulable state.

Over the long-term, the risk for clinical cardiac events in patients with no coronary artery abnormalities is similar to the general population. For patients in whom coronary artery abnormalities developed, the risk for cardiac complications, such as thrombosis, stenosis, myocardial infarction, and death, ranges between 1% and 48%. Follow-up is especially needed among the subset of patients with neutropenia who have been treated with IVIG. The administration of IVIG is shown to improve left ventricular function. The AHA recommends risk stratification based on the assessment of coronary luminal dimensions by echocardiogram, under cardiologic supervision. The frequency of clinical follow-up, diagnostic testing, reproductive counseling, indications for medical therapy (beta-blockers, statins), and thromboprophylaxis (aspirin

and anticoagulation) depends on the individual's risk assessment.

► When to Refer

All cases of Kawasaki disease merit referral to specialists.

Burns JC. Cyclosporine and coronary outcomes in Kawasaki disease. *J Pediatr.* 2019;210:239. [PMID: 31234982]

Centers for Disease Control and Prevention. Multisystem inflammatory syndrome in children. https://www.cdc.gov/coronavirus/2019-ncov/hcp/pediatric-hcp.html#anchor_1589580133375

Schroeder AR et al. COVID-19 and Kawasaki disease: finding the signal in the noise. *Hosp Pediatr.* 2020;10:e1. [PMID: 32404331]

Zheng X et al. Efficacy between low and high dose aspirin for the initial treatment of Kawasaki disease: current evidence based on a meta-analysis. *PLoS One.* 2019;14:e0217274. [PMID: 31117119]

Bacterial & Chlamydial Infections

Bryn A. Boslett, MD
Rachel Bystritsky, MD

33

INFECTIONS CAUSED BY GRAM-POSITIVE BACTERIA

STREPTOCOCCAL INFECTIONS

Group A beta-hemolytic streptococci (*Streptococcus pyogenes*) are the most common bacterial cause of pharyngitis. See Pharyngitis & Tonsillitis in Chapter 8.

1. Acute Rheumatic Fever & Scarlet Fever

► General Considerations

Group A streptococci producing erythrogenic toxin may cause scarlet fever in susceptible persons. Acute rheumatic fever may follow recurrent episodes of pharyngitis beginning 1–4 weeks after the onset of symptoms. Effectively controlling rheumatic fever depends on identification and treatment of primary streptococcal infection and secondary prevention of recurrences.

Glomerulonephritis is another rare complication, following a single infection with a nephritogenic strain of streptococcus group A (eg, types 4, 12, 2, 49, and 60), more commonly on the skin than in the throat, and begins 1–3 weeks after the onset of the infection.

► Clinical Findings

S. pyogenes (group A *Streptococcus* [GAS]) pharyngitis is usually a self-limited condition, lasting 3–5 days. The rash of scarlet fever (also called scarletina) is diffusely erythematous and resembles a sunburn, and superimposed fine red papules give the skin a sandpaper consistency; it is most intense in the groin and axillas. It blanches on pressure, may become petechial, and fades in 2–5 days, leaving a fine desquamation. The face is flushed, with circumoral pallor, and the tongue is coated with enlarged red papillae (strawberry tongue). The diagnosis is clinical in the setting of streptococcal pharyngitis. The diagnosis of acute rheumatic fever relies on a constellation of signs, symptoms, and laboratory findings, known as the **Jones criteria**: **major** criteria include presence of pancarditis, polyarthritis, subcutaneous nodules, erythema marginatum, chorea,

and **minor** criteria include presence of heart block, arthralgia, elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), fever, leukocytosis, or history of prior rheumatic fever. At least two major Jones criteria or one major and two minor criteria plus evidence of recent GAS infection by either bacterial culture data, rapid strep testing, or elevated anti-strep antibody titers are required to establish a diagnosis. These complications are more common in children.

► Treatment

Antimicrobial therapy of pharyngitis may reduce the risk of complications (see Chapter 8). There is no additional treatment of scarlet fever or acute rheumatic fever beyond that of the underlying streptococcal pharyngitis.

► Prevention of Recurrent Rheumatic Fever

Patients who have had rheumatic fever should be treated with a continuous course of antimicrobial prophylaxis for at least 5 years. Effective regimens are erythromycin, 250 mg orally twice daily, or penicillin G, 500 mg orally daily.

Karthikeyan G et al. Acute rheumatic fever. Lancet. 2018;392:161.
[PMID: 30025809]

2. Streptococcal Skin Infections

Group A beta-hemolytic streptococci are not normal skin flora. Streptococcal skin infections result from colonization of normal skin by contact with other infected individuals or by preceding streptococcal respiratory infection.

► Clinical Findings

A. Symptoms and Signs

Erysipelas is a painful superficial cellulitis that frequently involves the face (Figure 33–1). It is well demarcated from the surrounding normal skin. It affects skin with impaired lymphatic drainage, such as edematous lower extremities or wounds.



Figure 33–1. Erysipelas of the face with edema, bright red erythema, and serosanguineous discharge from the severely swollen cheek. (Public Health Image Library, CDC.)

Impetigo is a focal, vesicular, pustular lesion with a thick, amber-colored crust with a “stuck-on” appearance (see Chapter 6).

B. Laboratory Findings

Cultures obtained from a wound or pustule are likely to grow group A streptococci. Blood cultures are occasionally positive.

Table 33–1. Treatment of common skin and soft tissue infections (SSTIs).

SSTI Type	Common Pathogens	Treatment
Purulent (abscess, furuncle, carbuncle, cellulitis with purulence)	<i>Staphylococcus aureus</i>	<p>Incision and drainage is the primary treatment Consider the addition of antibiotics in select situations¹</p> <p>Oral antibiotic regimens²</p> <p>Dicloxacillin 500 mg four times daily or cephalexin 500 mg four times daily Clindamycin 300–450 mg three or four times daily or trimethoprim-sulfamethoxazole one double-strength tablet twice daily or doxycycline (or minocycline) 100 mg twice daily</p> <p>Intravenous antibiotic regimens²</p> <p>Nafcillin 1–2 g four to six times daily or cefazolin 1 g three times daily Vancomycin 1 g twice daily or daptomycin 4 mg/kg once daily Linezolid 600 mg (can also be given orally) twice daily for 10–14 days</p>
Nonpurulent (cellulitis, erysipelas)	Beta-hemolytic streptococci (<i>S aureus</i> less likely)	<p>Oral antibiotic regimens²</p> <p>Ampicillin 500 mg three times daily or 875 mg twice daily Cephalexin 500 mg four times daily or clindamycin 300 mg three times daily²</p> <p>Intravenous antibiotic regimens²</p> <p>Nafcillin 1–2 g four to six times daily or cefazolin 1 g three times daily Vancomycin 1 g twice daily or daptomycin 4 mg/kg once daily</p>

¹Antibiotic therapy should be given in addition to incision and drainage for purulent skin and soft tissue infections if the patient has any of the following: severe or extensive disease, symptoms and signs of systemic illness, purulent cellulitis/wound infection, comorbidities and extremes of age, abscess in area difficult to drain or on face/hand, associated septic phlebitis, or lack of response to incision and drainage alone. Antibiotic doses may vary based on weight and kidney function. Dosages listed assume normal renal and hepatic function, as well as average weight. Reevaluate dosing with renal/hepatic impairment.

²Other drugs that are FDA approved for treating SSTIs include daptomycin, 4 mg/kg intravenously once daily for 7–14 days; tedizolid 200 mg orally once daily for 6 days; tigecycline 100 mg intravenously once followed by 50 mg intravenously twice a day for 5–14 days; ceftaroline 600 mg twice a day for 7–14 days; dalbavancin 1500 mg as a single intravenous dose; oritavancin 1200 mg as a single intravenous dose; telavancin 10 mg/kg intravenously once daily for 7–14 days; and delafloxacin, 450 mg orally or 300 mg intravenously twice daily for 5–14 days.

Treatment

Although penicillin is the treatment of choice for streptococcal infections, it may be difficult to differentiate staphylococcal infections from streptococcal infections. In practice, initial therapy for patients with risk factors for *Staphylococcus aureus* (eg, injection drug use, diabetes mellitus, wound infection) should cover this organism. Either intravenous nafcillin or cefazolin (which can also be given intramuscularly) is a reasonable choice. In the patient at risk for methicillin-resistant *S aureus* infection or with a serious penicillin allergy (ie, anaphylaxis), intravenous vancomycin or daptomycin should be used (Table 33–1).

Patients who do not require parenteral therapy may be treated with amoxicillin, 500 mg three times daily or 875 mg twice daily for 7–10 days. A first-generation oral cephalosporin, eg, cephalexin, or clindamycin is an alternative to amoxicillin (Table 33–1). In patients with recurrent cellulitis of the leg, maintenance therapy (for at least 1 year) with penicillin, 250 mg orally twice daily, may reduce relapses.

Cranendonk DR et al. Cellulitis: current insights into pathophysiology and clinical management. *Neth J Med*. 2017;75:366. [PMID: 29219814]

Stevens DL et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2014;59:147. [PMID: 24947530]

3. Necrotizing Fasciitis

Necrotizing fasciitis is a rapidly spreading infection involving the fascia of deep muscle often involving an extremity,

head and neck, and perianal or genital area (“Fournier gangrene”). Some patients have a preceding skin or blunt trauma injury. Patients who are immunosuppressed, diabetic, at extremes of age (elderly or neonates), or affected by liver disease are generally more susceptible.

Distinguishing necrotizing fasciitis from necrotizing myositis may be difficult as skeletal muscle and fascia are involved in both syndromes. Necrotizing fasciitis is most often monomicrobial; the usual causative agent is *S pyogenes* (Group A beta-hemolytic streptococci) but it can also be caused by other streptococcal species, and occasionally by *S aureus*. Infections can be polymicrobial (mixed aerobic and anaerobic bacteria). A history of exposure to brackish water or marine life should raise suspicion for *Vibrio vulnificans* or *Aeromonas* species. Patients with burn injuries are susceptible to *Pseudomonas* species. Necrotizing myositis is often caused by *Clostridia* species (clostridial myonecrosis or “gas gangrene”). See Clostridial Diseases, below.

► Clinical Findings

A. Symptoms and Signs

The clinical findings at presentation may be those of severe cellulitis, but the presence of systemic toxicity and severe pain, which may be followed by anesthesia of the involved area due to destruction of nerves as infection advances through the fascial planes, is a clue to the diagnosis. Infection can progress rapidly, and pain often subsides as nerves are destroyed. Multiorgan failure is common as infection progresses.

B. Laboratory Findings

Nonspecific serum markers include elevated white blood cell count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Elevated creatine kinase may indicate muscle involvement. Blood cultures and wound cultures should be obtained, as well as tissue cultures from surgical specimens. Histologic specimens may demonstrate extensive tissue destruction, thrombosis of blood vessels, and bacteria spreading along fascial planes.

C. Imaging

CT or MRI of the affected area may show gas in tissues or fascial plane infection. Imaging may also appear normal, so rely on clinical suspicion and surgical evaluation.

► Treatment

Surgical exploration is mandatory when the diagnosis is suspected. Early and extensive debridement is essential for survival. Surgical evaluation should not be delayed while awaiting imaging or other diagnostic tests, especially in the setting of rapid progression of clinical manifestations.

Broad-spectrum antibiotic therapy should be initiated whenever the diagnosis is suspected and should cover aerobic and anaerobic organisms. Initial therapy typically consists of a carbapenem (meropenem or imipenem) or piperacillin-tazobactam plus an agent with activity against methicillin-resistant *S aureus* (vancomycin, linezolid, or

daptomycin) plus clindamycin for its antitoxin and other effects against toxin-producing strains of streptococci and staphylococci. Patients with exposure histories that suggest less common etiologies should have additional therapy targeted to those organisms. Antibiotic therapy should then be tailored to culture results. Antibiotic therapy should be continued until all infected tissue has been removed and the patient has stabilized; the final duration depends on individual patient factors.

In addition to surgical and antibiotic therapy, the use of intravenous immunoglobulin for streptococcal necrotizing soft tissue infections has been shown to reduce mortality. The dose is 1 g/kg on day 1, followed by 0.5 g/kg on days 2 and 3.

Bruun T et al. Risk factors and predictors of mortality in streptococcal necrotizing soft-tissue infections: a multicenter prospective study. Clin Infect Dis. 2021;72:293. [PMID: 31923305]

Stevens DL et al. Necrotizing soft-tissue infections. N Engl J Med. 2017;377:2253. [PMID: 29211672]

4. Other Group A Streptococcal Infections

Arthritis, pneumonia, empyema, endocarditis, and necrotizing fasciitis are relatively uncommon infections that may be caused by group A streptococci. Toxic shock-like syndrome also occurs.

Arthritis generally occurs in association with cellulitis. In addition to intravenous therapy with penicillin G, 2 million units every 4 hours (or cefazolin or vancomycin in doses recommended above for penicillin-allergic patients), frequent percutaneous needle aspiration should be performed to remove joint effusions. Open surgical drainage may be necessary in many cases. Treatment duration is not well studied but is generally 2–4 weeks, with final duration dependent upon clinical improvement and normalization of inflammatory markers (ESR, CRP).

Pneumonia and **empyema** often are characterized by extensive tissue destruction and an aggressive, rapidly progressive clinical course associated with significant morbidity and mortality. High-dose penicillin (as for group A streptococci endocarditis, below) and chest tube drainage are indicated for treatment of empyema. Vancomycin is an acceptable substitute in penicillin-allergic patients.

Group A streptococci can cause **endocarditis** in rare instances. Endocarditis should be treated with 4 million units of penicillin G intravenously every 4 hours for 4–6 weeks. Vancomycin, 1 g intravenously every 12 hours, is recommended for persons allergic to penicillin.

Any streptococcal infection—and necrotizing fasciitis in particular—can be associated with **streptococcal toxic shock syndrome**, typified by invasion of skin or soft tissues, acute respiratory distress syndrome, and kidney failure. Persons who are very young, older adults, and those with underlying medical conditions are at particularly high risk for invasive disease. Bacteremia occurs in most cases. Skin rash and desquamation may not be present. Mortality rates can be up to 80%. The syndrome is due to elaboration of pyrogenic erythrogenic toxin (which also

causes **scarlet fever**), a superantigen that stimulates massive release of inflammatory cytokines believed to mediate the shock. A beta-lactam, such as penicillin, remains the drug of choice for treatment of serious streptococcal infections, but clindamycin, which is a potent inhibitor of toxin production, should also be administered at a dose of 600 mg every 8 hours intravenously for invasive disease, especially in the presence of shock. Intravenous immune globulin can be considered for streptococcal toxic shock syndrome for possible therapeutic benefit from specific antibody to streptococcal exotoxins in immune globulin preparations. Many dosing regimens have been used, including 0.5 g/kg once daily for 5–6 days or a single dose of 2 g/kg with a repeat dose at 48 hours if the patient remains unstable.

Outbreaks of invasive disease have been associated with colonization by invasive clones that can be transmitted to close contacts who, though asymptomatic, may be a reservoir for disease. Tracing contacts of patients with invasive disease is controversial.

Gunderson CG et al. Do patients with cellulitis need to be hospitalized? A systematic review and meta-analysis of mortality rates of inpatients with cellulitis. *J Gen Intern Med*. 2018; 33:1553. [PMID: 30022408]

5. Non-Group A Streptococcal Infections

Non-group A hemolytic streptococci (eg, groups B, C, and G) produce a spectrum of disease similar to that of group A streptococci. The treatment of infections caused by these strains is similar to group A streptococci.

Group B streptococci are an important cause of sepsis, bacteremia, and meningitis in the neonate. Antepartum screening to identify carriers and peripartum antimicrobial prophylaxis are recommended in pregnancy. This organism, part of the normal vaginal flora, may cause septic abortion, endometritis, or peripartum infections and, less commonly, cellulitis, bacteremia, and endocarditis in adults. Treatment of infections caused by group B streptococci is with either penicillin or vancomycin in doses recommended for group A streptococci. Because of in vitro synergism, some experts recommend the addition of low-dose gentamicin, 1 mg/kg every 8 hours.

Viridans streptococci, which are nonhemolytic or alpha-hemolytic (ie, producing a green zone of hemolysis on blood agar), are part of the normal oral flora. Although these strains may produce focal pyogenic infection, they are most notable as the leading cause of native valve endocarditis.

Group D streptococci include *Streptococcus galloyticus (bovis)* and the enterococci. *S galloyticus (bovis)* is a cause of endocarditis in association with bowel neoplasia or cirrhosis and is treated like viridans streptococci.

Baddour LM et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015;132:1435. [PMID: 26373316]

Kim SL et al. Distribution of streptococcal groups causing infective endocarditis: a descriptive study. *Diagn Microbiol Infect Dis*. 2018;91:269. [PMID: 29567126]

ENTEROCOCCAL INFECTIONS

Two species, *Enterococcus faecalis* and *Enterococcus faecium*, are responsible for most human enterococcal infections. Enterococci cause wound infections, urinary tract infections, bacteremia, and endocarditis. Infections caused by penicillin-susceptible strains should be treated with ampicillin 2 g every 4 hours or penicillin 3–4 million units every 4 hours; if the patient is penicillin-allergic, vancomycin 15 mg/kg every 12 hours intravenously can be given. If the patient has endocarditis or meningitis, gentamicin 1 mg/kg every 8 hours intravenously should be added to the regimen for a duration of 2–3 weeks in order to achieve the bactericidal activity that is required to cure these infections. In cases of endocarditis, ceftriaxone 2 g every 12 hours may be given instead of gentamicin in combination with the ampicillin.

Resistance to vancomycin, penicillin, and gentamicin is common among enterococcal isolates, especially *E faecium*; it is essential to determine antimicrobial susceptibility of isolates. Infection control measures that may be indicated to limit their spread include isolation, barrier precautions, and avoidance of overuse of vancomycin and gentamicin. Consultation with an infectious diseases specialist is strongly advised when treating infections caused by resistant strains of enterococci. Quinupristin/dalfopristin and linezolid are approved by the FDA for treatment of infections caused by vancomycin-resistant strains of enterococci. Daptomycin, tigecycline, tedizolid, and oritavancin are not approved by the FDA for the treatment for vancomycin-resistant strains of enterococci, although they are frequently active in vitro.

Quinupristin/dalfopristin is not active against strains of *E faecalis* and should be used only for infections caused by *E faecium*. The dose is 7.5 mg/kg intravenously every 8–12 hours. Phlebitis and irritation at the infusion site (often requiring a central line) and an arthralgia-myalgia syndrome are relatively common side effects. Linezolid, an oxazolidinone, is active against both *E faecalis* and *E faecium*. The dose is 600 mg twice daily, and both intravenous and oral preparations are available. Its two principal side effects are thrombocytopenia and bone marrow suppression; however, peripheral neuropathy, optic neuritis, and lactic acidosis have been observed with prolonged use (typically greater than 6 weeks) due to mitochondrial toxicity. Emergence of resistance has occurred during therapy with both quinupristin/dalfopristin and linezolid.

Baddour LM et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015;132:1435. [PMID: 26373316]

PNEUMOCOCCAL INFECTIONS

1. Pneumococcal Pneumonia



ESSENTIALS OF DIAGNOSIS

- ▶ Productive cough, fever, rigors, dyspnea, early pleuritic chest pain.
- ▶ Consolidating lobar pneumonia on chest radiograph.
- ▶ Gram-positive diplococci on Gram stain of sputum.

► General Considerations

Pneumococcus is the most common cause of community-acquired pyogenic bacterial pneumonia. Alcoholism, asthma, HIV infection, sickle cell disease, splenectomy, and hematologic disorders are predisposing factors. Mortality rates remain high in cases of advanced age, multilobar disease, hypoxemia, extrapulmonary complications, and bacteremia.

► Clinical Findings

A. Symptoms and Signs

Presenting symptoms and signs include high fever, productive cough, occasional hemoptysis, and pleuritic chest pain. Rigors may occur initially but are uncommon later in the course. Bronchial breath sounds are an early sign.

B. Laboratory Findings

There is often leukocytosis, or occasionally leukopenia, but neither finding should be used to make a decision about hospital admission (see When to Admit, below).

Diagnosis requires isolation of the organism in culture, although the Gram stain appearance of sputum can be suggestive. Sputum and blood cultures, positive in 60% and 25% of cases of pneumococcal pneumonia, respectively, should be obtained prior to initiation of antimicrobial therapy in patients who are admitted to the hospital. A good-quality sputum sample (less than 10 epithelial cells and greater than 25 polymorphonuclear leukocytes per high-power field) shows gram-positive diplococci in 80–90% of cases. A rapid urinary antigen test for *Streptococcus pneumoniae*, with sensitivity of 70–80% and specificity greater than 95%, can assist with early diagnosis. The use of procalcitonin to guide therapy is discussed below.

C. Imaging

Pneumococcal pneumonia classically is a lobar pneumonia with radiographic findings of consolidation and occasionally effusion. However, differentiating it from other pneumonias is not possible radiographically or clinically because of significant overlap in presentations.

► Complications

Parapneumonic (sympathetic) effusion is common and may cause recurrence or persistence of fever. These sterile

fluid accumulations need no specific therapy. Empyema occurs in 5% or less of cases and is differentiated from sympathetic effusion clinically and by the presence of organisms on Gram-stained fluid or positive pleural fluid cultures.

Pneumococcal pericarditis is a rare complication that can cause tamponade. Pneumococcal arthritis also is uncommon. Pneumococcal endocarditis usually involves the aortic valve and often occurs in association with meningitis and pneumonia (sometimes referred to as Austrian or Osler triad). Early heart failure and multiple embolic events are typical.

► Treatment

A. Specific Measures

Initial antimicrobial therapy for pneumonia is empiric (see Table 9–9) pending isolation and identification of the causative agent. Once *S pneumoniae* is identified as the infecting pathogen, any of several antimicrobial agents may be used depending on the clinical setting, community patterns of penicillin resistance, and susceptibility of the particular isolate.

1. Outpatient therapy—Uncomplicated pneumococcal pneumonia (ie, arterial Po_2 greater than 60 mm Hg, no coexisting medical problems, and single-lobe disease without signs of extrapulmonary infection) caused by penicillin-susceptible strains of pneumococcus may be treated on an outpatient basis with amoxicillin, 750 mg orally twice daily for 7–10 days. Cephalosporins including cefpodoxime, 200 mg orally twice daily, and cefdinir, 300 mg twice daily, may also be used. For penicillin-allergic patients, alternatives are azithromycin, one 500-mg dose orally on the first day and 250 mg for the next 4 days; clarithromycin, 500 mg orally twice daily for 7 days; doxycycline, 100 mg orally twice daily for 7 days; levofloxacin, 750 mg orally for 5–7 days; or moxifloxacin, 400 mg orally for 7–14 days. Patients should be monitored for clinical response (eg, less cough, defervescence within 2–3 days) because pneumococci have become increasingly resistant to penicillin and the second-line agents.

Outpatients with high-risk comorbid conditions (such as pulmonary disease, diabetes, cardiac disease, or alcohol use disorder) may benefit from broader combination therapy (eg, amoxicillin/clavulanate or cephalosporin plus doxycycline or a macrolide), unless a fluoroquinolone is chosen for monotherapy.

2. Inpatient therapy—Parenteral therapy is generally recommended for the hospitalized patient at least until there has been clinical improvement. Ceftriaxone, 1 g intravenously every 24 hours, is effective for strains that are penicillin-susceptible (ie, strains for which the minimum inhibitory concentration [MIC] of penicillin is 2 mcg/mL or less for non-CNS specimens). For serious penicillin allergy or infection caused by a highly penicillin-resistant strain, vancomycin, 1 g intravenously every 12 hours, is effective. Additionally, azithromycin or doxycycline is typically added for coverage of atypical organisms. Alternatively, a respiratory fluoroquinolone (eg, levofloxacin,

750 mg) can be used. The total duration of therapy is not well defined but 5–7 days is appropriate for patients who have an uncomplicated infection and demonstrate a good clinical response. Corticosteroid use remains controversial in community-acquired pneumonia and should not be administered routinely.

Procalcitonin is a peptide released by human cells in response to exposure to bacterial toxins and is measurable in the serum. In trials, antibiotics have been safely held or withdrawn when the procalcitonin level was normal or decreasing by a substantial amount. Antibiotic consumption is significantly reduced in patients presenting with acute respiratory infections and sepsis when guided by procalcitonin levels; procalcitonin can be used effectively in these settings only when used as a point of care test.

B. Treatment of Complications

Pleural effusions developing after initiation of antimicrobial therapy usually are sterile, and thoracentesis need not be performed if the patient is otherwise improving. Thoracentesis is indicated for an effusion present prior to initiation of therapy and in the patient who has not responded to antibiotics after 3–4 days. Chest tube drainage may be required if pneumococci are identified by culture or Gram stain, especially if aspiration of the fluid is difficult.

Echocardiography should be done if pericardial effusion is suspected. Patients with pericardial effusion who are responding to antibiotic therapy and have no signs of tamponade may be monitored and treated with indomethacin, 50 mg orally three times daily, for pain. In patients with increasing effusion, unsatisfactory clinical response, or evidence of tamponade, pericardiocentesis will determine whether the pericardial space is infected. Infected fluid must be drained either percutaneously (by tube placement or needle aspiration), by placement of a pericardial window, or by pericardectomy. Pericardectomy eventually may be required to prevent or treat constrictive pericarditis.

Endocarditis should be treated for 4 weeks with 3–4 million units of penicillin G every 4 hours intravenously; ceftriaxone, 2 g once daily intravenously; or vancomycin, 15 mg/kg every 12 hours intravenously. Mild heart failure due to valvular regurgitation may respond to medical therapy, but moderate to severe heart failure is an indication for prosthetic valve implantation, as are systemic emboli or large friable vegetations as determined by echocardiography.

C. Penicillin-Resistant Pneumococci

Resistance breakpoints for parenterally administered penicillin and high-dose oral amoxicillin (2 g twice daily) are as follows: susceptible, penicillin MIC of 2 mcg/mL or less; intermediate, MIC of 4 mcg/mL; resistant, MIC of 8 mcg/mL or more. Note, however, that these breakpoints do not apply to orally administered penicillin, which are the same as for use of penicillin in treatment of meningitis. In cases of pneumococcal pneumonia where the isolate has a penicillin MIC greater than 2 mcg/mL, cephalosporin cross-resistance is common, and a non-β-lactam antimicrobial,

such as vancomycin, 1 g intravenously every 12 hours, or a fluoroquinolone with enhanced gram-positive activity (eg, levofloxacin, 750 mg intravenously or orally once daily, or moxifloxacin, 400 mg intravenously or orally once daily), is recommended. Penicillin-resistant strains of pneumococci may be resistant to macrolides, trimethoprim-sulfamethoxazole, and chloramphenicol, and susceptibility must be documented prior to their use. All blood and cerebrospinal fluid isolates should still be tested for resistance to penicillin. There has been no change to the penicillin susceptibility breakpoint for pneumococcal isolates causing meningitis, nor any change in treatment recommendations.

► Prevention

See Chapter 30 for discussion of pneumococcal vaccines. All patients should have screening for smoking cessation.

► When to Refer

- All patients with suspected pneumococcal endocarditis or meningitis need infectious disease specialist consultation.
- Extensive disease.
- Seriously ill patient with pneumonia, particularly in the setting of comorbid conditions (eg, liver disease).
- Progression of pneumonia or failure to improve on antibiotics.

► When to Admit

- All patients in whom pneumococcal endocarditis or meningitis is suspected or documented should be admitted for observation and empiric therapy.
- All patients with pneumococcal pneumonia that is multilobar or is associated with significant hypoxemia.
- Failure of outpatient pneumonia therapy, including inability to maintain oral intake and medications.
- Exacerbations of underlying disease (eg, heart failure) by pneumonia that would benefit from hospitalization.
- Risk scores for illness severity using PSI (Pneumonia Severity Index) ([https://www.thecalculator.co/health/Pneumonia-Severity-Index-\(PSI\)-Calculator-977.html](https://www.thecalculator.co/health/Pneumonia-Severity-Index-(PSI)-Calculator-977.html)) and CURB-65 (Confusion, Urea, Respiratory rate, Blood Pressure, Age ≥ 65 years) (<https://www.mdcalc.com/curb-65-score-pneumonia-severity>) can aid in the decision about whether to admit a patient.

Galán-Ros J et al. Bacteremic pneumococcal pneumonia in adults. *Arch Bronconeumol*. 2018;54:54. [PMID: 28757279]

Hill AT et al; CHEST Expert Cough Panel. Adult outpatients with acute cough due to suspected pneumonia or influenza: CHEST guideline and Expert Panel report. *Chest*. 2019; 155:155. [PMID: 30296418]

Huang DT et al; ProACT Investigators. Procalcitonin-guided use of antibiotics for lower respiratory tract infection. *N Engl J Med*. 2018;379:236. [PMID: 29781385]

Wunderink RG et al. Advances in the causes and management of community acquired pneumonia in adults. *BMJ*. 2017; 358:j2471. [PMID: 28694251]

2. Pneumococcal Meningitis



ESSENTIALS OF DIAGNOSIS

- ▶ Fever, headache, altered mental status.
- ▶ Meningismus.
- ▶ Gram-positive diplococci on Gram stain of cerebrospinal fluid.

► General Considerations

S pneumoniae is the most common cause of bacterial meningitis in adults. Head trauma with cerebrospinal fluid leaks, sinusitis, and pneumonia may precede it.

► Clinical Findings

A. Symptoms and Signs

The onset is rapid, with fever, headache, meningismus, and altered mentation. Pneumonia may be present. Compared with meningitis caused by the meningococcus, pneumococcal meningitis lacks a rash. Obtundation, focal neurologic deficits, and cranial nerve palsies are more prominent features and may lead to long-term sequelae.

B. Laboratory Findings

The cerebrospinal fluid has typically greater than 1000 white blood cells/mcL ($1 \times 10^9/L$), over 60% of which are polymorphonuclear leukocytes; the glucose concentration is less than 40 mg/dL (2.22 mmol/L), or less than 50% of the simultaneous serum concentration; and the protein usually exceeds 150 mg/dL (1500 mg/L). Not all cases of meningitis will have these typical findings, and alterations in cerebrospinal fluid cell counts and chemistries may be surprisingly minimal, overlapping with those of aseptic meningitis.

Gram stain of cerebrospinal fluid shows gram-positive cocci in 80–90% of cases, and in untreated cases, blood or cerebrospinal fluid cultures are almost always positive. Urine antigen tests may be positive but are not sufficiently sensitive to exclude the diagnosis.

► Treatment

Antibiotics should be given as soon as the diagnosis is suspected. If lumbar puncture must be delayed (eg, while awaiting results of an imaging study to exclude a mass lesion), the patient should be treated empirically for presumed meningitis with intravenous ceftriaxone, 2 g, plus vancomycin, 15 mg/kg, plus dexamethasone, 0.15 mg/kg administered concomitantly after blood cultures (positive in 50% of cases) have been obtained. Once susceptibility to penicillin has been confirmed, penicillin, 24 million units intravenously daily in six divided doses, or ceftriaxone, 2 g every 12 hours intravenously, is continued for 10–14 days in documented cases.

The best therapy for penicillin-resistant strains is not known. Penicillin-resistant strains (MIC greater than

0.06 mcg/mL) are often cross-resistant to the third-generation cephalosporins as well as other antibiotics. Susceptibility testing is essential to proper management of this infection. If the MIC of ceftriaxone or cefotaxime is 0.5 mcg/mL or less, single-drug therapy with either of these cephalosporins is likely to be effective; when the MIC is 1 mcg/mL or more, treatment with a combination of ceftriaxone, 2 g intravenously every 12 hours, plus vancomycin, 30 mg/kg/day intravenously in two or three divided doses, is recommended. If a patient with a penicillin-resistant organism is slow to respond clinically, repeat lumbar puncture may be indicated to assess bacteriologic response.

Dexamethasone administered with antibiotic to adults has been associated with a 60% reduction in mortality and a 50% reduction in unfavorable outcomes. It is recommended that dexamethasone be given immediately prior to or concomitantly with the first dose of appropriate antibiotic and continued in those with pneumococcal disease every 6 hours thereafter for a total of 4 days. The effect of dexamethasone on outcome of meningitis caused by penicillin-resistant organisms is not known.

Costerus JM et al. Community-acquired bacterial meningitis. Curr Opin Infect Dis. 2017;30:135. [PMID: 27828810]
Mora Carpio AL et al. Pneumococcal bacteremia and meningitis. N Engl J Med. 2018;379:2063. [PMID: 30462944]

STAPHYLOCOCCUS AUREUS INFECTIONS

1. Skin & Soft Tissue Infections



ESSENTIALS OF DIAGNOSIS

- ▶ Localized erythema with induration and purulent drainage.
- ▶ Abscess formation.
- ▶ Folliculitis commonly observed.
- ▶ Gram stain of pus shows gram-positive cocci in clusters; cultures usually positive.

► General Considerations

Approximately one-quarter of people are asymptomatic nasal carriers of *S aureus*, which is spread by direct contact. Carriage often precedes infection, which occurs as a consequence of disruption of the cutaneous barrier or impairment of host defenses. *S aureus* tends to cause more purulent skin infections than streptococci, and abscess formation is common. The prevalence of methicillin-resistant strains in many communities is high and should influence antibiotic choices when antimicrobial therapy is needed.

► Clinical Findings

A. Symptoms and Signs

S aureus skin infections may begin around one or more hair follicles, causing folliculitis; may become localized to



▲ Figure 33–2. Methicillin-resistant *Staphylococcus aureus* (MRSA) abscess on the back of the neck. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

form boils (or furuncles); or may spread to adjacent skin and deeper subcutaneous tissue (ie, a carbuncle). Deep abscesses involving muscle or fascia may occur, often in association with a deep wound or other inoculation or injection (Figure 33–2). Necrotizing fasciitis, a rare form of *S aureus* skin and soft tissues infection, has been reported with community strains of methicillin-resistant *S aureus*.

B. Laboratory Findings

Cultures of the wound or abscess material will almost always yield the organism. In patients with systemic signs of infection, blood cultures should be obtained because of potential bacteremia, endocarditis, osteomyelitis, or metastatic seeding of other sites. Patients who are bacteremic should have blood cultures taken early during therapy to exclude persistent bacteremia, an indicator of severe or complicated infection.

► Treatment

Proper drainage of abscess fluid or other focal infections is the mainstay of therapy. Incision and drainage alone is highly effective for the treatment of most uncomplicated cutaneous abscesses. A small benefit can be obtained from the addition of antimicrobials following incision and drainage (Table 33–1). In areas where methicillin resistance among community *S aureus* isolates is high, recommended oral antimicrobial agents include clindamycin, trimethoprim-sulfamethoxazole, doxycycline, or minocycline. When the risk of methicillin resistance is low or methicillin susceptibility has been confirmed by testing of the isolate, consider dicloxacillin or cephalexin. Seven days of treatment are sufficient in most cases.

For complicated infections with extensive cutaneous or deep tissue involvement or fever, initial parenteral therapy is often indicated. When methicillin resistance rates are high (above 10%), empiric therapy with vancomycin is a drug of choice. Cefazolin intravenously or intramuscularly

or a penicillinase-resistant penicillin such as nafcillin or oxacillin in a dosage of 1.5 g every 6 hours intravenously is preferred for infections caused by methicillin-susceptible isolates. Total duration of therapy for soft tissue infections depends on clinical response and effectiveness of drainage/debridement. Courses of 7 days with early transition to oral therapy are effective in many cases.

Linezolid is FDA approved for treatment of skin and skin-structure infections as well as hospital-acquired pneumonia caused by methicillin-resistant strains of *S aureus*; it is clinically as effective as vancomycin for these indications. Its considerable cost makes it an unattractive choice for most routine outpatient infections, and its safety in treatment courses lasting longer than 2–3 weeks is not well characterized. Other drugs that are FDA approved for treating skin and soft tissue infections are listed in Table 33–1. Telavancin is approved for the treatment of hospital-acquired *S aureus* pneumonia but has been associated with nephrotoxicity.

Khan A et al. Current and future treatment options for community-associated MRSA infection. *Expert Opin Pharmacother*. 2018;19:457. [PMID: 29480032]

Moran GJ et al. Effect of cephalexin plus trimethoprim-sulfamethoxazole vs cephalexin alone on clinical cure of uncomplicated cellulitis: a randomized clinical trial. *JAMA*. 2017; 317:2088. [PMID: 28535235]

Pullman J et al; PROCEED Study Group. Efficacy and safety of delafloxacin compared with vancomycin plus aztreonam for acute bacterial skin and skin structure infections: a phase 3, double-blind, randomized study. *J Antimicrob Chemother*. 2017;72:3471. [PMID: 29029278]

Talan DA et al. Trimethoprim-sulfamethoxazole versus placebo for uncomplicated skin abscess. *N Engl J Med*. 2016;374:823. [PMID: 26962903]

2. Osteomyelitis

S aureus causes approximately 60% of all cases of osteomyelitis. Osteomyelitis may be caused by direct inoculation, eg, from an open fracture or as a result of surgery; by extension from a contiguous focus of infection or open wound; or by hematogenous spread. Long bones and vertebrae are the usual sites. Epidural abscess is a common complication of vertebral osteomyelitis and should be suspected if fever and severe back or neck pain are accompanied by radicular pain or symptoms or signs indicative of spinal cord compression (eg, incontinence, extremity weakness, pathologic extremity reflexes).

► Clinical Findings

A. Symptoms and Signs

The infection may be acute, with abrupt development of local symptoms and systemic toxicity, or indolent, with insidious onset of vague pain over the site of infection, progressing to local tenderness and constitutional symptoms (fever, malaise, anorexia, night sweats). Fever is absent in one-third or more of cases. Back pain is often the only symptom in vertebral osteomyelitis and may be associated with an epidural abscess and spinal cord compression. Draining sinus tracts occur in chronic infections or infections of foreign body implants.

B. Laboratory Findings

The diagnosis is established by isolation of *S aureus* from the blood, bone, or a contiguous focus of a patient with symptoms and signs of focal bone infection. Blood culture will be positive in approximately 60% of untreated cases. Bone biopsy and culture are indicated if blood cultures are sterile. Inflammatory markers (CRP, ESR) are typically elevated.

C. Imaging

Bone scan and gallium scan, each with a sensitivity of approximately 95% and a specificity of 60–70%, are useful in identifying or confirming the site of bone infection. Plain bone films early in the course of infection are often normal but will become abnormal in most cases even with effective therapy. Spinal infection (unlike malignancy) traverses the disk space to involve the contiguous vertebral body. CT is more sensitive than plain films and helps localize associated abscesses. MRI is slightly less sensitive than bone scan, but has a specificity of 90%. It is indicated when epidural abscess is suspected in association with vertebral osteomyelitis. ¹⁸F-FDG-PET/CT may be useful in the diagnosis of vertebral osteomyelitis as well as the detection of other metastatic sites of infection.

Treatment

Prolonged therapy is required to cure staphylococcal osteomyelitis. Durations of 4–6 weeks or longer are recommended. Traditionally, intravenous therapy has been preferred, particularly during the acute phase of the infection for patients with systemic toxicity. Intravenous therapy with cefazolin, 2 g every 8 hours, or alternatively, nafcillin or oxacillin, 9–12 g/day in six divided doses, are the drugs of choice for infection with methicillin-sensitive isolates. Patients with infections due to methicillin-resistant strains of *S aureus* or who have severe penicillin allergies should be treated with vancomycin, 30 mg/kg/day intravenously divided in two or three doses. Doses should be adjusted to achieve a vancomycin trough level of 15–20 mcg/mL. Studies have also demonstrated noninferiority of oral regimens following 2 weeks of intravenous therapy. In patients with *S aureus* isolates susceptible to oral agents, combination oral therapy has been shown to be effective if given for 4–6 weeks following 2 weeks of induction therapy with an intravenous agent as above. Levofloxacin, 750 mg orally daily, or ciprofloxacin, 750 mg orally twice daily, in combination with rifampin, 300 mg twice daily, is an oral regimen with the most data supporting efficacy. Trimethoprim-sulfamethoxazole, doxycycline, or clindamycin may be an option for oral therapy in the right candidate; consultation with an infectious diseases specialist is recommended. The role of newer agents, such as daptomycin or linezolid, remains to be defined.

Surgical treatment is often indicated under the following circumstances: (1) staphylococcal osteomyelitis with associated epidural abscess and spinal cord compression, (2) other abscesses (psoas, paraspinal), (3) extensive disease, or (4) recurrent or persistent infection despite

standard medical therapy. Follow-up imaging may not be needed in patients who demonstrate improvement in symptoms and normalization of inflammatory markers.

Barberi EF et al. 2015 Infectious Diseases Society of America (IDSA) clinical practice guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults. Clin Infect Dis. 2015;61:e26. [PMID: 26229122]

Li HK et al; OVIVA Trial Collaborators. Oral versus intravenous antibiotics for bone and joint infection. N Engl J Med. 2019; 380:425. [PMID: 30699315]

3. Staphylococcal Bacteremia

S aureus readily invades the bloodstream and infects sites distant from the primary site of infection. Whenever *S aureus* is recovered from blood cultures, the possibility of endocarditis, osteomyelitis, or other metastatic deep infection must be considered. Bacteremia that persists for more than 48–96 hours after initiation of therapy is strongly predictive of worse outcome and complicated infection. Given the relatively high risk of infective endocarditis in patients with *S aureus* bacteremia, transesophageal echocardiography is recommended for most patients as a sensitive and cost-effective method for excluding underlying endocarditis. However, transthoracic echocardiography may be sufficient in select patients considered to be at low risk for endocarditis, namely those who meet all the following criteria: (1) no permanent intracardiac device, (2) sterile follow-up blood cultures within 4 days after the initial set, (3) no hemodialysis dependence, (4) nosocomial acquisition of *S aureus* bacteremia, and (5) no clinical signs of infective endocarditis or secondary foci of infection.

Empiric therapy of staphylococcal bacteremia should be with vancomycin, 15–20 mg/kg/dose intravenously every 8–12 hours, or daptomycin, 6 mg/kg/day intravenously, until results of susceptibility tests are known. If the *S aureus* isolate is methicillin-susceptible, treatment should be narrowed to cefazolin, 2 g every 8 hours, or nafcillin or oxacillin, 2 g intravenously every 4 hours. Cefazolin is as effective as nafcillin or oxacillin and has been associated with fewer adverse events during treatment. In patients with methicillin-resistant *S aureus*, treatment should be with vancomycin, 15–20 mg/kg/dose intravenously every 8–12 hours. Maintaining a vancomycin trough concentration of 15–20 mcg/mL may improve outcomes and is recommended. Daptomycin 6 mg/kg/day is also an FDA-approved option as long as the patient does not require treatment for concomitant *S aureus* pneumonia. The addition of rifamycins to standard antimicrobial therapy has not been shown to be beneficial in the absence of indwelling prosthetic material and is associated with more adverse events. Duration of therapy for *S aureus* bacteremia is 4–6 weeks of antibiotic therapy but a subset of patients with uncomplicated infection may be able to be treated for 14 days. A patient with uncomplicated bacteremia must meet all the following criteria: (1) infective endocarditis has been excluded, (2) no implanted prostheses are present, (3) follow-up blood cultures drawn 2–4 days after the initial set are sterile, (4) the patient defervesces within 72 hours of initiation of effective antibiotic therapy, and (5)

no evidence of metastatic infection is present on examination. When present at the time of diagnosis, central venous catheters should be removed. Vancomycin treatment failures are relatively common, particularly for complicated bacteremia and among infections involving foreign bodies. Improved outcomes have been demonstrated when consultation with an infectious diseases specialist is obtained and should be considered in all cases of *S aureus* bacteremia.

Li J et al. β -Lactam therapy for methicillin-susceptible *Staphylococcus aureus* bacteremia: a comparative review of cefazolin versus antistaphylococcal penicillins. *Pharmacotherapy*. 2017;37:346. [PMID: 28035690]

Liu C et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis*. 2011;52:e18. [PMID: 21208910]

Rao SN et al. Treatment outcomes with cefazolin versus oxacillin for deep-seated methicillin-susceptible *Staphylococcus aureus* bloodstream infections. *Antimicrob Agents Chemother*. 2015;59:5232. [PMID: 26077253]

4. Toxic Shock Syndrome

S aureus produces toxins that cause three important entities: “scalded skin syndrome” in children, toxic shock syndrome in adults, and enterotoxin food poisoning. Toxic shock syndrome is characterized by abrupt onset of high fever, vomiting, and watery diarrhea. Sore throat, myalgias, and headache are common. Hypotension with kidney and heart failure is associated with a poor outcome. A diffuse macular erythematous rash and nonpurulent conjunctivitis are common, and desquamation, especially of palms and soles, is typical during recovery (Figure 33–3). Fatality rates may be as high as 15%. Although originally associated with tampon use, any focus (eg, nasopharynx, bone, vagina, rectum, abscess, or wound) harboring a toxin-producing *S aureus* strain can cause toxic shock syndrome. Classically, blood cultures are negative because symptoms are due to the effects of the toxin and not systemic infection. Other entities associated with toxic shock include invasive group A streptococcal infection and certain *Clostridium* species (*C perfringens*, *C sordellii*).



▲ **Figure 33–3.** Marked desquamation due to toxic shock syndrome, which develops late in the disease. (Public Health Image Library, CDC.)

Important aspects of treatment include rapid rehydration, targeted antimicrobials (antistaphylococcal therapy when *S aureus* is implicated) (Table 33–1), management of kidney or heart failure, and addressing sources of toxin, eg, removal of tampon or drainage of abscess. Intravenous clindamycin, 900 mg every 8 hours, is often added to inhibit toxin production. Intravenous immune globulin may be considered, although there are limited data compared with *Streptococcus* toxic shock syndrome (see above).

5. Infections Caused by Coagulase-Negative Staphylococci

Coagulase-negative staphylococci are an important cause of infections of intravascular and prosthetic devices and of wound infection following cardiothoracic surgery. These organisms infrequently cause infections such as osteomyelitis and endocarditis in the absence of a prosthesis. Most human infections are caused by *Staphylococcus epidermidis*, *S haemolyticus*, *S hominis*, *S warneri*, *S saprophyticus*, *S saccharolyticus*, and *S cohnii*. These common hospital-acquired pathogens are less virulent than *S aureus*, and infections caused by them tend to be more indolent.

Because coagulase-negative staphylococci are normal inhabitants of human skin, it is difficult to distinguish infection from contamination, the latter perhaps accounting for three-fourths of blood culture isolates. Infection is more likely if the patient has a foreign body (eg, sternal wires, prosthetic joint, prosthetic cardiac valve, pacemaker, intracranial pressure monitor, cerebrospinal fluid shunt, peritoneal dialysis catheter) or an intravascular device in place. Purulent or serosanguineous drainage, erythema, pain, or tenderness at the site of the foreign body or device suggests infection. Joint instability and pain are signs of prosthetic joint infection. Fever, a new murmur, instability of the prosthesis, or signs of systemic embolization are evidence of prosthetic valve endocarditis.

Infection is also more likely if the same strain is consistently isolated from two or more blood cultures (particularly if samples were obtained at different times) and from the foreign body site. Contamination is more likely when a single blood culture is positive or if more than one strain is isolated from blood cultures. The antimicrobial susceptibility pattern and speciation are used to determine whether one or more strains have been isolated.

Whenever possible, the intravascular device or foreign body suspected of being infected should be removed. However, removal and replacement of some devices (eg, prosthetic joint, prosthetic valve, cerebrospinal fluid shunt) can be a difficult or risky procedure, and it may sometimes be preferable to treat with antibiotics alone, knowing that the probability of cure is reduced and that surgical management may eventually be necessary.

Coagulase-negative staphylococci are commonly resistant to beta-lactams and multiple other antibiotics. For patients with normal kidney function, vancomycin, 1 g intravenously every 12 hours, is the treatment of choice until susceptibility to penicillinase-resistant penicillins or other agents has been confirmed. Duration of therapy has not been established for relatively uncomplicated infections, such as those from intravenous devices, which may

be eliminated by simply removing the device. Infection involving bone or a prosthetic valve should be treated for 6 weeks. A combination regimen of vancomycin plus rifampin, 300 mg orally twice daily, plus gentamicin, 1 mg/kg intravenously every 8 hours, is recommended for treatment of prosthetic valve endocarditis caused by methicillin-resistant strains.

Baddour LM et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015;132:1435. [PMID: 26373316]

Tan EM et al. Outcomes in patients with cardiovascular implantable electronic device infection managed with chronic antibiotic suppression. *Clin Infect Dis*. 2017;64:1516. [PMID: 28329125]

CLOSTRIDIAL DISEASES

1. Clostridial Myonecrosis (Gas Gangrene)



ESSENTIALS OF DIAGNOSIS

- ▶ Sudden onset of pain and edema in and around a contaminated wound.
- ▶ Prostration and systemic toxicity.
- ▶ Brown to blood-tinged watery exudate, with skin discoloration of surrounding area.
- ▶ Gas in the tissue by palpation or radiograph.
- ▶ Gram-positive rods in culture or smear of exudate.

General Considerations

Gas gangrene or clostridial myonecrosis is a life-threatening muscle infection produced by any one of several clostridia (*Clostridium perfringens*, *C ramosum*, *C bifermentans*, *C histolyticum*, *C novyi*, etc). Trauma and injection drug use are common predisposing conditions. Toxins produced in devitalized tissues under anaerobic conditions result in shock, hemolysis, and myonecrosis.

Clinical Findings

A. Symptoms and Signs

The onset is usually sudden, with rapidly increasing pain in the affected area, hypotension, and tachycardia. Fever is present but is not proportionate to the severity of the infection. In the last stages of the disease, severe prostration, stupor, delirium, and coma occur.

The wound becomes swollen, and the surrounding skin is pale. There is a foul-smelling brown, blood-tinged serous discharge. As the disease advances, the surrounding tissue changes from pale to dusky and finally becomes deeply discolored, with coalescent, red, fluid-filled vesicles. Gas may be palpable in the tissues.

B. Laboratory Findings

Gas gangrene is a clinical diagnosis, and empiric therapy is indicated if the diagnosis is suspected. Radiographic studies may show gas within the soft tissues, but this finding is not sensitive nor specific. The smear shows absence of neutrophils and the presence of gram-positive rods. Anaerobic culture confirms the diagnosis.

Differential Diagnosis

Other bacteria can produce gas in infected tissue, eg, enteric gram-negative organisms, or anaerobes.

Treatment

Adequate surgical debridement and exposure of infected areas are essential, with radical surgical excision often necessary. Penicillin, 2 million units every 3 hours intravenously, is an effective adjunct. Clindamycin may decrease the production of bacterial toxin, and some experts recommend the addition of clindamycin, 600–900 mg every 8 hours intravenously, to penicillin. Hyperbaric oxygen therapy has been used empirically but must be used in conjunction with administration of an appropriate antibiotic and surgical debridement.

De Prost N et al. Therapeutic targets in necrotizing soft tissue infections. *Intensive Care Med*. 2017;43:1717. [PMID: 28474117]

Stevens DL et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2014;59:147. [PMID: 24947530]

Yang Z et al. Interventions for treating gas gangrene. *Cochrane Database Syst Rev*. 2015;12:CD010577. [PMID: 26631369]

2. Tetanus



ESSENTIALS OF DIAGNOSIS

- ▶ History of wound and possible contamination.
- ▶ Jaw muscle stiffness ("lock jaw"), then spasms (trismus).
- ▶ Neck stiffness, dysphagia, irritability, hyperreflexia.
- ▶ Finally, painful convulsions precipitated by minimal stimuli.

General Considerations

Tetanus is caused by the neurotoxin tetanospasmin, elaborated by *C tetani*. Spores of this organism are ubiquitous in soil and may germinate when introduced into a wound. Tetanospasmin interferes with neurotransmission at spinal synapses of inhibitory neurons. As a result, minor stimuli result in uncontrolled spasms, and reflexes are exaggerated. The incubation period is 5 days to 15 weeks, with the average being 8–12 days.

Most cases occur in unvaccinated individuals. Persons at risk are older adults, migrant workers, newborns, and

injection drug users. While puncture wounds are particularly prone to causing tetanus, any wound, including bites or decubiti, may become colonized and infected by *C. tetani*.

► Clinical Findings

A. Symptoms and Signs

The first symptom may be pain and tingling at the site of inoculation, followed by spasticity of the muscles nearby. Stiffness of the jaw, neck stiffness, dysphagia, and irritability are other early signs. Hyperreflexia develops later, with spasms of the jaw muscles (trismus) or facial muscles and rigidity and spasm of the muscles of the abdomen, neck, and back. Painful tonic convulsions precipitated by minor stimuli are common. Spasms of the glottis and respiratory muscles may cause acute asphyxia. The patient is awake and alert throughout the illness. The sensory examination is normal. The temperature is normal or only slightly elevated.

B. Laboratory Findings

The diagnosis of tetanus is made clinically.

► Differential Diagnosis

Tetanus must be differentiated from various acute central nervous system (CNS) infections such as meningitis. Trismus may occasionally develop with the use of phenothiazines. Strychnine poisoning should also be considered.

► Complications

Airway obstruction is common. Urinary retention and constipation may result from spasm of the sphincters. Respiratory arrest and cardiac failure are late events.

► Prevention

Active immunization prevents tetanus (see Table 30–7). For primary immunization of adults, Td (tetanus and diphtheria toxoids vaccine) is administered as two doses 4–6 weeks apart, with a third dose 6–12 months later. For one of the three doses, Tdap (tetanus toxoid, reduced-dose diphtheria

toxoid, acellular pertussis vaccine) should be substituted for Td. Booster Td doses are given every 10 years or at the time of major injury if it occurs more than 5 years after a dose; a single dose of Tdap is preferred to Td for wound management if the patient has not been previously vaccinated with Tdap. Women should receive Tdap with each pregnancy, preferably between 27 and 36 weeks, with immunization at 27–30 weeks associated with the highest antibody concentrations.

Passive immunization with tetanus immune globulin, 250 units intramuscularly, should be used in nonimmunized individuals and those whose immunization status is uncertain whenever a wound is contaminated or likely to have devitalized tissue. Active immunization with tetanus toxoid vaccine is started concurrently. Table 33–2 provides a guide to prophylactic management.

► Treatment

A. Specific Measures

Human tetanus immune globulin, 500 units, should be administered intramuscularly within the first 24 hours of presentation. Whether intrathecal administration has any additional benefit is controversial. An unblinded, randomized trial comparing intramuscular tetanus immune globulin to intramuscular plus intrathecal tetanus immune globulin found clinical benefit in the intrathecal group. However, the exact immune globulin preparation was not specified and the total dose was 4000 units. Tetanus does not produce natural immunity, and a full course of immunization with tetanus toxoid should be administered once the patient has recovered.

B. General Measures

Debridement of wounds should be undertaken if implicated as the source. Metronidazole, 7.5 mg/kg administered intravenously or orally every 6 hours (maximum 4 g daily), is preferred and should be administered to all patients. Penicillin, 20 million units intravenously daily in divided doses, is an alternative. Minimal stimuli can provoke spasms, so the patient should be placed at bed rest

Table 33–2. Guide to tetanus prophylaxis in wound management.

History of Absorbed Tetanus Toxoid	Clean, Minor Wounds		All Other Wounds ¹	
	Tdap or Td ²	TIG ³	Tdap or Td ²	TIG ³
Unknown or < 3 doses	Yes	No	Yes	Yes
3 or more doses	No ⁴	No	No ⁵	No

¹Examples include wounds contaminated with dirt, feces, soil, or saliva; puncture wounds; avulsions; and wounds from missiles, crushing, burns, and frostbite.

²Td indicates tetanus toxoid and diphtheria toxoid vaccine, adult form. Tdap indicates tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine, which may be substituted as a single dose for Td. Unvaccinated individuals should receive a complete series of three doses, one of which is Tdap.

³Human tetanus immune globulin, 250 units intramuscularly.

⁴Yes if more than 10 years have elapsed since last dose.

⁵Yes if more than 5 years have elapsed since last dose. (More frequent boosters are not needed and can enhance side effects.) Tdap has been safely administered within 2 years of Td vaccination, although local reactions to the vaccine may be increased.

and monitored under the quietest conditions possible. Sedation, paralysis with curare-like agents, and mechanical ventilation are often necessary. Enteral nutritional support should be given early.

► Prognosis

High mortality rates are associated with a short incubation period, early onset of convulsions, and delay in treatment. Contaminated lesions about the head and face are more dangerous than wounds elsewhere.

Healy CM et al. Association between third-trimester Tdap immunization and neonatal pertussis antibody concentration. *JAMA*. 2018;320:1464. [PMID: 30304426]

3. Botulism



ESSENTIALS OF DIAGNOSIS

- ▶ Recent ingestion of home-canned or smoked foods; recovery of toxin in serum or food.
- ▶ Injection drug use.
- ▶ Diplopia, dry mouth, dysphagia, dysphonia; muscle weakness leading to respiratory paralysis; normal sensory examination.
- ▶ Pupils are fixed and dilated in most cases.

► General Considerations

Botulism is a paralytic disease caused by botulinum toxin, which is produced by *Clostridium botulinum*, a ubiquitous, strictly anaerobic, spore-forming bacillus found in soil. Four toxin types—A, B, E, and F—cause human disease. Botulinum toxin is extremely potent and is classified by the CDC as a high-priority agent because of its potential for use as an agent of bioterrorism. Naturally occurring botulism exists in three forms: food-borne botulism, infant botulism, or wound botulism. Food-borne botulism is caused by ingestion of preformed toxin present in canned, smoked, or vacuum-packed foods such as home-canned vegetables, smoked meats, and vacuum-packed fish. Commercial foods have been associated with outbreaks of botulism. Infant botulism (associated with ingestion of honey) and wound botulism (often occurs in association with injection drug use) result from organisms present in the gut or wound that secrete toxin.

► Clinical Findings

A. Symptoms and Signs

Twelve to 36 hours after ingestion of the toxin, visual disturbances appear, particularly diplopia and loss of accommodation. Ptosis, cranial nerve palsies with impairment of extraocular muscles, and fixed dilated pupils are characteristic signs. The sensory examination is normal. Other symptoms are dry mouth, dysphagia, and dysphonia. Nausea and vomiting may be present, particularly with type E

toxin. The sensorium remains clear and the temperature normal. Paralysis progressing to respiratory failure and death may occur unless mechanical assistance is provided.

B. Laboratory Findings

Toxin in foods and patients' serum can be demonstrated by mouse inoculation and identified with specific antiserum.

► Differential Diagnosis

Because the clinical presentation of botulism is so distinctive and the differential diagnosis limited, botulism once considered is not easily confused with other diseases. Cranial nerve involvement may be seen with vertebrobasilar insufficiency, the C. Miller Fisher variant of Guillain-Barré syndrome, myasthenia gravis, or any basilar meningitis (infectious or carcinomatous).

► Treatment

If botulism is suspected, the clinician should contact state health authorities or the CDC for advice and help with procurement of equine serum heptavalent botulism antitoxin and for assistance in obtaining assays for toxin in serum, stool, or food. Skin testing is recommended to exclude hypersensitivity to the antitoxin preparation. Antitoxin should be administered as early as possible, ideally within 24 hours of the onset of symptoms, to arrest progression of disease; its administration should not be delayed for laboratory confirmation of the diagnosis. Respiratory failure is managed with intubation and mechanical ventilation. Parenteral fluids or alimentation should be given while swallowing difficulty persists. The removal of unabsorbed toxin from the gut may be attempted. Remnants of suspected foods should be assayed for toxin. Persons who might have eaten the suspected food must be located and observed.

Adalja AA et al. Clinical management of potential bioterrorism-related conditions. *N Engl J Med*. 2015;372:954. [PMID: 25738671]

Schulte M et al. Effective and rapid treatment of wound botulism, a case report. *BMC Surg*. 2017;17:103. [PMID: 29073888]

LISTERIOSIS



ESSENTIALS OF DIAGNOSIS

- ▶ Ingestion of contaminated food product.
- ▶ Fever in a pregnant woman in her third trimester.
- ▶ Altered mental status and fever in an elderly or immunocompromised patient.
- ▶ Blood and cerebrospinal fluid cultures confirm the diagnosis.

► General Considerations

Listeria monocytogenes is a facultative, motile, gram-positive rod that is capable of invading several cell types and

causes intracellular infection. Most cases of infection caused by *L monocytogenes* are sporadic, but outbreaks have been traced to eating contaminated food, including unpasteurized dairy products, hot dogs, delicatessen meats, cantaloupes, and ricotta cheese. Outbreaks have been associated with significant morbidity and mortality in infected persons.

Clinical Findings

Five types of infection are recognized:

(1) **Infection during pregnancy**, usually in the last trimester, is a mild febrile illness without an apparent primary focus and may resolve without specific therapy. However, approximately one in five pregnancies complicated by listeriosis result in spontaneous abortion or stillbirth and surviving infants are at risk for clinical neonatal listeriosis.

(2) **Granulomatosis infantisepticum** is a neonatal infection acquired in utero, characterized by disseminated abscesses, granulomas, and a high mortality rate.

(3) **Bacteremia** with or without sepsis syndrome is an infection of neonates or immunocompromised adults. The presentation is of a febrile illness without a recognized source.

(4) **Meningitis** caused by *L monocytogenes* affects infants under 2 months of age as well as older adults, ranking third after pneumococcus and meningococcus as common causes of bacterial meningitis. Cerebrospinal fluid shows a *neutrophilic* pleocytosis. Adults with meningitis are often immunocompromised, and cases have been associated with HIV infection and therapy with tumor necrosis factor (TNF) inhibitors such as infliximab.

(5) **Focal infections**, including adenitis, brain abscess, endocarditis, osteomyelitis, and arthritis, occur rarely.

Prevention

At-risk patients (eg, pregnant women) should avoid unpasteurized milk products. Smoked seafoods, cold cuts, hot dogs, and meat spreads also carry risk. Thoroughly cook animal source food and wash raw vegetables.

Treatment

Ampicillin, 8–12 g/day intravenously in four to six divided doses (the higher dose for meningitis), is the treatment of choice. Gentamicin, 5 mg/kg/day intravenously once or in divided doses, is synergistic with ampicillin against *Listeria* in vitro and in animal models, and the use of combination therapy may be considered during the first few days of treatment to enhance eradication of organisms. In patients with penicillin allergies, trimethoprim-sulfamethoxazole has excellent intracellular and cerebrospinal fluid penetration and is an appropriate alternative. The dose is 10–20 mg/kg/day intravenously of the trimethoprim component. Mortality and morbidity rates still are high. Therapy should be administered for at least 2–3 weeks. Longer durations—between 3 and 6 weeks—have been recommended for treatment of meningitis, especially in immunocompromised persons.

- Madjunkov M et al. Listeriosis during pregnancy. *Arch Gynecol Obstet*. 2017;296:143. [PMID: 28536811]
Salama PJ et al. Learning from listeria: safer food for all. *Lancet*. 2018;391:2305. [PMID: 29900862]

INFECTIVE ENDOCARDITIS



- ▶ Fever.
- ▶ Preexisting organic heart lesion.
- ▶ Positive blood cultures.
- ▶ Evidence of vegetation on echocardiography.
- ▶ Evidence of systemic emboli.

General Considerations

Endocarditis is a bacterial or fungal infection of the valvular or endocardial surface of the heart. The clinical presentation depends on the infecting organism and the valve or valves that are infected. More virulent organisms—*S aureus* in particular—tend to produce a more rapidly progressive and destructive infection. Endocarditis caused by more virulent organisms often presents as an acute febrile illness and is complicated by early embolization, acute valvular regurgitation, and myocardial abscess formation. Viridans strains of streptococci, enterococci, other bacteria, yeasts, and fungi tend to cause a more subacute picture.

Predisposing valvular abnormalities include rheumatic involvement of any valve, bicuspid aortic valves, calcific or sclerotic aortic valves, hypertrophic subaortic stenosis, mitral valve prolapse, and a variety of congenital disorders such as ventricular septal defect, tetralogy of Fallot, coarctation of the aorta, or patent ductus arteriosus. Rheumatic disease is no longer the major predisposing factor in developed countries. Regurgitation lesions are more susceptible than stenotic ones.

The initiating event in native valve endocarditis is colonization of the valve by bacteria or yeast that gain access to the bloodstream. Transient bacteremia is common during dental, upper respiratory, urologic, and lower gastrointestinal diagnostic and surgical procedures. It is less common during upper gastrointestinal and gynecologic procedures. Intravascular devices are also a portal of access of microorganisms into the bloodstream. A large proportion of cases of *S aureus* endocarditis are attributable to health care-associated bacteremia.

Native valve endocarditis is usually caused by *S aureus*, viridans streptococci, enterococci, or HACEK organisms (an acronym for *Haemophilus aphrophilus* [now *Aggregatibacter aphrophilus*], *Actinobacillus actinomycetemcomitans* [now *Aggregatibacter actinomycetemcomitans*], *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species). Streptococcal species formerly accounted for the majority of native valve endocarditis cases; *S aureus* is now the leading cause. Gram-negative organisms and fungi account for a small percentage.

In injection drug users, *S aureus* accounts for over 60% of all endocarditis cases and for 80–90% of cases in which the tricuspid valve is infected. Enterococci and streptococci comprise most of the balance in about equal proportions. Other causative organisms are gram-negative aerobic bacilli, fungi, and unusual organisms.

The microbiology of **prosthetic valve endocarditis** also is distinctive. Early infections (ie, those occurring within 2 months after valve implantation) are commonly caused by staphylococci—both coagulase-positive and coagulase-negative—gram-negative organisms, and fungi. In late prosthetic valve endocarditis, streptococci are commonly identified, although coagulase-negative and coagulase-positive staphylococci still cause many cases.

► Clinical Findings

A. Symptoms and Signs

Virtually all patients have fever at some point in the illness, although it may be very low grade (less than 38°C) in elderly individuals and in patients with heart failure or kidney failure. Rarely, there may be no fever at all.

The duration of illness typically is a few days to a few weeks. Nonspecific symptoms are common. The initial symptoms and signs of endocarditis may be caused by direct arterial, valvular, or cardiac damage. Although a changing regurgitant murmur is significant diagnostically, it is the exception rather than the rule. Symptoms also may occur as a result of embolization, metastatic infection or immunologically mediated phenomena. These include cough; dyspnea; arthralgias or arthritis; diarrhea; and abdominal, back, or flank pain.

The characteristic peripheral lesions—petechiae (on the palate or conjunctiva or beneath the fingernails), subungual (“splinter”) hemorrhages (Figure 33–4), Osler nodes (painful, violaceous raised lesions of the fingers, toes, or feet, Janeway lesions (painless erythematous lesions of the palms or soles), and Roth spots (exudative lesions in the retina)—occur in about 25% of patients. Strokes and major systemic embolic events are present in about 25% of patients and tend to occur before or within the first week of antimicrobial therapy. Hematuria and proteinuria may result from emboli or immunologically mediated glomerulonephritis.

B. Imaging

Chest radiograph may show evidence for the underlying cardiac abnormality and, in right-sided endocarditis, pulmonary infiltrates. The electrocardiogram is nondiagnostic, but new conduction abnormalities suggest myocardial abscess formation. Echocardiography is useful in identifying vegetations and other characteristic features suspicious for endocarditis and may provide adjunctive information about the specific valve or valves that are infected. The sensitivity of transthoracic echocardiography is between 55% and 65%; it cannot reliably rule out endocarditis but may confirm a clinical suspicion. Transesophageal echocardiography is 90% sensitive in detecting vegetations and is particularly useful for identifying valve ring abscesses as well as prosthetic valve endocarditis.



▲ **Figure 33–4.** Splinter hemorrhages appearing as red lineal streaks under the nail plate and within the nail bed, in endocarditis, psoriasis, and trauma. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

C. Diagnostic Studies

1. Blood cultures—Three sets of blood cultures are recommended before starting antibiotics to maximize microbiologic diagnosis; adequate volume is important. Each culture bottle should be filled with 10 mL of blood since half of adults have less than 1 colony forming unit of bacteria per mL blood. The yield of bacteria may be up to 5% higher for every additional milliliter collected. Optimal yield is with two or three sets of cultures from different sites. There is no difference in yield if blood is collected simultaneously or several hours apart.

Approximately 5% of cases will be culture-negative, usually attributable to administration of antimicrobials prior to cultures. If antimicrobial therapy has been administered prior to obtaining cultures and the patient is clinically stable, it is reasonable to withhold antimicrobial therapy for 2–3 days so that appropriate cultures can be obtained. Culture-negative endocarditis may also be due to organisms that require special media for growth (eg, *Legionella*, *Bartonella*, *Abiotrophia* species, formerly referred to as nutritionally deficient streptococci), organisms that do not grow on artificial media (*Tropheryma whipplei*, or pathogens of Q fever or psittacosis), or those that may require prolonged incubation (eg, *Brucella*, anaerobes, HACEK organisms). *Bartonella quintana* is an important cause of culture-negative endocarditis.

2. Modified Duke criteria—The Modified Duke criteria are useful for the diagnosis of endocarditis. **Major criteria** include (1) two positive blood cultures for a microorganism that typically causes infective endocarditis or persistent bacteremia, or a single positive blood culture for

Coxiella burnetii or anti-phase 1 IgG antibody titer greater than or equal to 1:800; and (2) evidence of endocardial involvement documented by echocardiography showing definite vegetation, myocardial abscess, new partial dehiscence of a prosthetic valve, or new valvular regurgitation (increase or change in murmur is not sufficient). **Minor criteria** include the presence of a predisposing condition; fever of 38°C or higher; vascular phenomena, such as cutaneous hemorrhages, aneurysm, systemic emboli, or pulmonary infarction; immunologic phenomena, such as glomerulonephritis, Osler nodes, Roth spots, or rheumatoid factor; and positive blood cultures not meeting the major criteria or serologic evidence of an active infection. A definite diagnosis can be made with 80% accuracy if two major criteria, one major criterion and three minor criteria, or five minor criteria are fulfilled. A possible diagnosis of endocarditis is made if one major and one minor criterion or three minor criteria are met. If fewer criteria are found, or a sound alternative explanation for illness is identified, or the patient's febrile illness has resolved within 4 days, endocarditis is unlikely.

► Complications

The course of infective endocarditis is determined by the degree of damage to the heart, by the site of infection (right-sided versus left-sided, aortic versus mitral valve), by the presence of metastatic foci of infection, by the occurrence of embolization, and by immunologically mediated processes. Destruction of infected heart valves is especially common and precipitous with *S aureus*, but can occur with any organism and can progress even after bacteriologic cure. The infection can also extend into the myocardium, resulting in abscesses leading to conduction disturbances, and involving the wall of the aorta, creating sinus of Valsalva aneurysms.

Peripheral embolization to the brain and myocardium may result in infarctions. Embolization to the spleen and kidneys is also common. Peripheral emboli may initiate metastatic infections or may become established in vessel walls, leading to mycotic aneurysms. Right-sided endocarditis (usually the tricuspid valve) causes septic pulmonary emboli, occasionally with infarction and lung abscesses.

► Prevention

The American Heart Association recommends antibiotic prophylaxis for infective endocarditis in a relatively small group of patients with predisposing congenital or valvular anomalies (Table 33–3) undergoing select dental procedures, operations involving the respiratory tract, or operations of infected skin, skin structure, or musculoskeletal tissue (Table 33–4). Current antimicrobial recommendations are given in Table 33–5.

► Treatment

Empiric regimens for endocarditis while culture results are pending should include agents active against staphylococci, streptococci, and enterococci. Vancomycin 1 g every 12 hours intravenously plus ceftriaxone 2 g every 24 hours

Table 33–3. Cardiac conditions with high risk of adverse outcomes from endocarditis for which prophylaxis with dental procedures is recommended.^{1,2}

Prosthetic cardiac valve
Previous infective endocarditis
Congenital heart disease (CHD) ³
Unrepaired cyanotic CHD, including palliative shunts and conduits
Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure ⁴
Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device
Cardiac transplantation recipients in whom cardiac valvulopathy develops

¹Reproduced, with permission, from Wilson W et al. Prevention of infective endocarditis. Circulation. 2007;116:1736. Copyright © 2007 American Heart Association, Inc.

²See Table 33–5 for prophylactic regimens.

³Except for the conditions listed above, antibiotic prophylaxis is not recommended for other forms of CHD.

⁴Prophylaxis is recommended because endothelialization of prosthetic material occurs within 6 months after procedure.

provides appropriate coverage pending definitive diagnosis; consultation with an infectious disease expert is strongly recommended when initiating treatment. Intravenous therapy has been the mainstay of treatment for infective endocarditis. Some data, however, have begun to support the use of oral antibiotic therapy following 2 weeks of intravenous antibiotic regimens for certain organisms.

Table 33–4. Recommendations for administration of bacterial endocarditis prophylaxis for patients according to type of procedure.¹

Prophylaxis Recommended	Prophylaxis Not Recommended
Dental procedures All dental procedures that involve manipulation of gingival tissue or the periapical region of the teeth or perforation of the oral mucosa, including routine cleaning	Dental procedures Routine anesthetic injections through noninfected tissue, taking dental radiographs, placement of removable prosthodontic or orthodontic appliances, adjustment of orthodontic appliances, placement of orthodontic brackets, shedding of deciduous teeth, and bleeding from trauma to the lips or oral mucosa
Respiratory tract procedures Only respiratory tract procedures that involve incision of the respiratory mucosa	Gastrointestinal tract procedures Genitourinary tract procedures
Procedures on infected skin, skin structure, or musculoskeletal tissue	

¹Reproduced, with permission, from Wilson W et al. Prevention of infective endocarditis. Circulation. 2007;116:1736. Copyright © 2007 American Heart Association, Inc.

Table 33–5. American Heart Association recommendations for endocarditis prophylaxis for dental procedures for patients with cardiac conditions.^{1–3}

Oral	Amoxicillin	2 g 1 hour before procedure
Penicillin allergy	Clindamycin or Cephalexin or Azithromycin or clarithromycin	600 mg 1 hour before procedure 2 g 1 hour before procedure (contraindicated if there is history of a beta-lactam immediate hypersensitivity reaction) 500 mg 1 hour before procedure
	Ampicillin	2 g intramuscularly or intravenously 30 minutes before procedure
	Clindamycin or Cefazolin	600 mg intravenously 1 hour before procedure 1 g intramuscularly or intravenously 30 minutes before procedure (contraindicated if there is history of a beta-lactam immediate hypersensitivity reaction)
Parenteral		

¹Data from the American Heart Association. Circulation. 2007;116:1736.

²For patients undergoing respiratory tract procedures involving incision of respiratory tract mucosa to treat an established infection or a procedure on infected skin, skin structure, or musculoskeletal tissue known or suspected to be caused by *S aureus*, the regimen should contain an anti-staphylococcal penicillin (eg, nafcillin 2 g intravenously 30 minutes prior to procedure) or cephalosporin (eg, cephalexin or cefazolin, dosed as per above). Vancomycin can be used to treat patients unable to tolerate a beta-lactam or if the infection is known or suspected to be caused by a methicillin-resistant strain of *S aureus*.

³See Table 33–3 for list of cardiac conditions.

A. Viridans Streptococci

For penicillin-susceptible viridans streptococcal endocarditis (ie, MIC 0.1 mcg/mL or less), penicillin G, 18 million units intravenously either continuously or in four to six equally divided doses, or ceftriaxone, 2 g intravenously once daily for 4 weeks, is recommended. The duration of therapy can be shortened to 2 weeks if gentamicin, 3 mg/kg intravenously every 24 hours, is used with penicillin or ceftriaxone. The 2-week regimen is reasonable and can be considered in patients with uncomplicated endocarditis, rapid response to therapy, and no underlying kidney disease. For the patient unable to tolerate penicillin or ceftriaxone, vancomycin, 15 mg/kg intravenously every 12 hours for 4 weeks, is given with a desired trough level of 10–15 mcg/mL. Prosthetic valve endocarditis is treated with a 6-week course of penicillin or ceftriaxone and the clinician can consider adding 2 weeks of gentamicin at the start of therapy.

Viridans streptococci relatively resistant to penicillin (ie, MIC greater than 0.12 mcg/mL but less than or equal to 0.5 mcg/mL) should be treated for 4 weeks. Penicillin G, 24 million units intravenously either continuously or in four to six equally divided doses, is combined with gentamicin, 3 mg/kg intravenously every 24 hours for the first 2 weeks. Ceftriaxone may be a reasonable alternative treatment option for isolates that are susceptible to ceftriaxone. In the patient with IgE-mediated allergy to penicillin, vancomycin alone, 15 mg/kg intravenously every 12 hours for 4 weeks, should be administered. Prosthetic valve endocarditis is treated with a 6-week course of penicillin or ceftriaxone plus gentamicin as above.

Endocarditis caused by viridans streptococci with an MIC greater than 0.5 mcg/mL or by *Abiotrophia* species should be treated the same as enterococcal endocarditis.

B. Other Streptococci

Endocarditis caused by *S pneumoniae*, group A streptococci (*S pyogenes*), or groups B, C, and G streptococci is unusual. *S pneumoniae* sensitive to penicillin (MIC less than 0.1 mcg/mL) can be treated with penicillin, 18 million units intravenously either continuously or in four to six equally divided doses, or cefazolin, 6 g intravenously either continuously or in three equally divided doses, or ceftriaxone, 2 g daily intravenously for 4 weeks. High-dose penicillin (24 million units) or a third-generation cephalosporin may be required for the treatment of endocarditis (without meningitis) caused by strains resistant to penicillin (MIC greater than 0.1 mcg/mL). The addition of vancomycin and rifampin to ceftriaxone may be considered in patients with *S pneumoniae* strains with cefotaxime MIC greater than 2 mcg/mL. Group A streptococcal infection can be treated with penicillin or ceftriaxone for 4–6 weeks. Groups B, C, and G streptococci tend to be more resistant to penicillin than group A streptococci, and some experts have recommended adding gentamicin, 3 mg/kg intravenously every 24 hours, to penicillin for the first 2 weeks of a 4- to 6-week course. Endocarditis caused by *S gallolyticus (bovis)* is associated with liver disease, especially cirrhosis, and gastrointestinal abnormalities, especially colon cancer. Colonoscopy should be performed to exclude the latter.

C. Group D Streptococci (Enterococci)

For enterococcal endocarditis, penicillin or ampicillin alone is inadequate. One recommended regimen is ampicillin, 2 g intravenously every 4 hours, or penicillin G, 18–30 million units intravenously continuously or in six equally divided doses plus gentamicin, 1 mg/kg intravenously every 8 hours. The second recommended regimen is ampicillin (2 g intravenously every 4 hours) plus ceftriaxone 2 g intravenously every 12 hours. The recommended duration of therapy is 4–6 weeks (the longer duration for patients with symptoms for more than 3 months, relapse, or prosthetic valve endocarditis). The combination of ampicillin plus ceftriaxone is recommended for patients with creatinine clearance less than 50 mL/min or whose enterococcal isolates are resistant to gentamicin. In patients intolerant of penicillin and ampicillin or who have enterococcal isolate resistant to these agents, vancomycin plus gentamicin can be used.

Endocarditis caused by strains resistant to penicillin and vancomycin are difficult to treat and should always be managed with an infectious diseases specialist.

D. Staphylococci

For methicillin-susceptible *S aureus* isolates, nafcillin or oxacillin, 12 g intravenously daily given continuously or in four to six divided doses, or cefazolin, 6 g intravenously daily given continuously or in three divided doses for 6 weeks, is the preferred therapy. In cases of brain abscess resulting from methicillin-susceptible *S aureus* endocarditis, nafcillin should be used instead of cefazolin. For patients with history of immediate type hypersensitivity to beta-lactams, a desensitization protocol should be undertaken. For patients with a history of non-anaphylactoid reactions to penicillins, cefazolin should be used. Patients who are infected with methicillin-resistant *S aureus* or who are unable to tolerate beta-lactam therapy should receive vancomycin, 30 mg/kg/day intravenously divided in two or three doses, to achieve a goal trough level of 15–20 mcg/kg, or daptomycin intravenously at greater than or equal to 8 mg/kg/day. Aminoglycoside combination regimens are not recommended. The effect of rifampin with antistaphylococcal drugs is variable, and its routine use is not recommended.

Because coagulase-negative staphylococci—a common cause of prosthetic valve endocarditis—are routinely resistant to methicillin, beta-lactam antibiotics should not be used for this infection unless the isolate is demonstrated to be susceptible. A combination of vancomycin, 30 mg/kg/day intravenously divided in two or three doses for 6 weeks; rifampin, 300 mg every 8 hours for 6 weeks; and gentamicin, 3 mg/kg intravenously every 8 hours for the first 2 weeks, is recommended for prosthetic valve infection. If the organism is sensitive to methicillin, either nafcillin or oxacillin or cefazolin can be used in combination with rifampin and gentamicin. Combination therapy with nafcillin or oxacillin (vancomycin or daptomycin for methicillin-resistant strains), rifampin, and gentamicin is also recommended for treatment of *S aureus* prosthetic valve infection.

E. HACEK Organisms

HACEK organisms are slow-growing, fastidious gram-negative coccobacilli or bacilli (*H aphrophilus* [now *A aphrophilus*], *A actinomycetemcomitans*, *C hominis*, *E corrodens*, and *Kingella* species) that are normal oral flora and cause less than 5% of all cases of endocarditis. They may produce beta-lactamase, and thus the treatment of choice is ceftriaxone (or another third-generation cephalosporin), 2 g intravenously once daily for 4 weeks. Prosthetic valve endocarditis should be treated for 6 weeks. In the penicillin-allergic patient, experience is limited, but fluoroquinolones have in vitro activity and should be considered.

F. Culture-Negative Endocarditis

Failure to culture microorganisms from patients with suspected infective endocarditis may be due to infection from organisms not recovered in routine microbiology testing or previous administration of antimicrobial agents before blood cultures were obtained. These cases must be managed with the assistance of an infectious disease specialist. Pathogens that are not able to be cultured by commonly used techniques include *Bartonella* species, *Chlamydia* species, *Brucella* species, and *Tropheryma whipplei*. Serologic testing should be performed in patients who have epidemiologic risk factors for these infections. Treatment should be directed at likely pathogens while awaiting serologic results; treatment of patients given prior antimicrobials before cultures were obtained must also consider likely pathogens.

G. Role of Surgery

While many cases can be successfully treated medically, operative management is frequently required. Acute heart failure unresponsive to medical therapy is an indication for valve replacement even if active infection is present. Infections unresponsive to appropriate antimicrobial therapy after 7–10 days (ie, persistent fevers, positive blood cultures despite therapy) are more likely to be eradicated if the valve is replaced. Surgery is nearly always required for cure of fungal endocarditis and is more often necessary with highly resistant bacteria. It is also indicated when the infection involves the sinus of Valsalva or produces septal abscesses. Recurrent infection with the same organism prompts an operative approach, especially with infected prosthetic valves. Continuing embolization presents a difficult problem when the infection is otherwise responding; surgery may be the proper approach. Particularly challenging is a large and fragile vegetation demonstrated by echocardiography in the absence of embolization. Most clinicians favor an operative approach with vegetectomy and valve repair if the patient is a good candidate. Operation without delay may be considered in patients with endocarditis and an embolic stroke who have an indication for surgery. If not urgent or if intracranial hemorrhage is present, a delay of at least 4 weeks should be considered. Embolization after bacteriologic cure does not necessarily imply recurrence of endocarditis.

H. Role of Anticoagulation

Anticoagulation is contraindicated in native valve endocarditis because of an increased risk of intracerebral hemorrhage from mycotic aneurysms or embolic phenomena. The role of anticoagulant therapy during prosthetic valve endocarditis is more controversial. Reversal of anticoagulation may result in thrombosis of the mechanical prosthesis, particularly in the mitral position. Conversely, anticoagulation during active prosthetic valve endocarditis caused by *S aureus* has been associated with fatal intracerebral hemorrhage. One approach is to discontinue anticoagulation during the septic phase of *S aureus* prosthetic valve endocarditis. In patients with *S aureus* prosthetic valve endocarditis complicated by a CNS embolic event, anticoagulation should be discontinued for the first 2 weeks of therapy. Indications for anticoagulation following prosthetic valve implantation for endocarditis are the same as for patients with prosthetic valves without endocarditis (eg, nonporcine mechanical valves and valves in the mitral position).

► Response to Therapy

If infection is caused by viridans streptococci, enterococci, or coagulase-negative staphylococci, defervescence occurs in 3–4 days on average; with *S aureus* or *Pseudomonas aeruginosa*, fever may persist for longer. Blood cultures should be obtained every 1–2 days to document sterilization. Other causes of persistent fever are myocardial or metastatic abscess, sterile embolization, superimposed hospital-acquired infection, and drug reaction. Most relapses occur within 1–2 months after completion of therapy. Obtaining one or two blood cultures during this period is prudent.

► When to Refer

- Consider consulting an infectious diseases specialist in all cases of suspected infective endocarditis.
- Consult a cardiac surgeon in the situations mentioned in the Role of Surgery section above to prevent further embolic disease, heart failure, and other complications, including death.

► When to Admit

Patients with infective endocarditis should be hospitalized for expedited evaluation and treatment.

Baddour LM et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. Circulation. 2015;132:1435. [PMID: 26373316]

Iversen K et al. Partial oral versus intravenous antibiotic treatment of endocarditis. N Engl J Med. 2019;380:415. [PMID: 30152252]

Vincent LL et al. Infective endocarditis: update on epidemiology, outcomes and management. Curr Cardiol Rep. 2018;20:86. [PMID: 30117004]

Wilson W et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation. 2007;116:1736. [PMID: 17446442]

INFECTIONS CAUSED BY GRAM-NEGATIVE BACTERIA

BORDETELLA PERTUSSIS INFECTION (Whooping Cough)

► ESSENTIALS OF DIAGNOSIS

- Predominantly in infants under age 2 years; adolescents and adults are reservoirs of infection.
- Two-week prodromal catarrhal stage of malaise, cough, coryza, and anorexia.
- Paroxysmal cough ending in a high-pitched inspiratory “whoop.”
- Absolute lymphocytosis, often striking; culture confirms diagnosis.

► General Considerations

Pertussis is an acute infection of the respiratory tract caused by *B pertussis* that is transmitted by respiratory droplets. The incubation period is 7–17 days. Half of all cases occur before age 2 years. Neither immunization nor disease confers lasting immunity to pertussis. Consequently, adults are an important reservoir of the disease.

► Clinical Findings

The symptoms of classic pertussis last about 6 weeks and are divided into three consecutive stages. The catarrhal stage is characterized by its insidious onset, with lacrimation, sneezing, and coryza, anorexia and malaise, and a hacking night cough that becomes diurnal. The paroxysmal stage is characterized by bursts of rapid, consecutive coughs followed by a deep, high-pitched inspiration (whoop). The convalescent stage begins 4 weeks after onset of the illness with a decrease in the frequency and severity of paroxysms of cough. The diagnosis often is not considered in adults, who may not have a typical presentation. Cough persisting more than 2 weeks is suggestive. Infection may also be asymptomatic.

The white blood cell count is usually 15,000–20,000/mcL ($15\text{--}20 \times 10^9/\text{L}$) (rarely, as high as 50,000/mcL [$50 \times 10^9/\text{L}$] or more), 60–80% of which are lymphocytes. The diagnosis is established by isolating the organism from a nasopharyngeal culture on special medium (eg, Bordet-Gengou agar). Polymerase chain reaction assays for *B pertussis* may be available in some clinical or health department laboratories.

► Prevention

Acellular pertussis vaccine is recommended for all infants, combined with diphtheria and tetanus toxoids (DTaP). Infants and susceptible adults with significant exposure should receive prophylaxis with an oral macrolide. In recognition of their importance as a reservoir of disease, vaccination of adolescents and adults against pertussis is recommended (see Table 30–7 and www.cdc.gov/vaccines/schedules). Adolescents aged 11–18 years (preferably between 11 and 12 years of age) who have completed the DTP or DTaP vaccination series should receive a single dose of either Tdap product instead of Td (tetanus and diphtheria toxoids vaccine) for booster immunization against tetanus, diphtheria, and pertussis. Tdap, which immunizes against the same bacteria as DTaP, is a booster immunization; Tdap contains the same amount of tetanus toxoid (T) as DTaP but reduced diphtheria toxoid and acellular pertussis (hence the lower case -dap). Adults of all ages (including those older than age 64 years) should receive a single dose of Tdap. In addition, pregnant women should receive a dose of Tdap during each pregnancy regardless of prior vaccination history, ideally between 27 and 36 weeks of gestation, to maximize the antibody response of the woman and the passive antibody transfer to the infant. For any woman who was not previously vaccinated with Tdap and for whom the vaccine was not given during her pregnancy, Tdap should be administered immediately postpartum. The CDC has eliminated the recommendation that a 2-year period window is needed between receiving the Td and Tdap vaccines based on data showing that there is not an increased risk of adverse events.

► Treatment

Antibiotic treatment should be initiated in all suspected cases. Treatment options include erythromycin, 500 mg four times a day orally for 7 days; azithromycin, 500 mg orally on day 1 and 250 mg for 4 more days; or clarithromycin, 500 mg orally twice daily for 7 days. Trimethoprim-sulfamethoxazole, 160–800 mg orally twice a day for 7 days, also is effective. Treatment shortens the duration of carriage and may diminish the severity of coughing paroxysms. These same regimens are indicated for prophylaxis of contacts to an active case of pertussis who are exposed within 3 weeks of the onset of cough in the index case.

DeSilva M et al. Tdap vaccination during pregnancy and microcephaly and other structural birth defects in offspring. *JAMA*. 2016;316:1823. [PMID: 27802536]

Nguyen VTN et al. Pertussis: the whooping cough. *Prim Care*. 2018;45:423. [PMID: 30115332]

OTHER BORDETELLA INFECTIONS

Bordetella bronchiseptica is a pleomorphic gram-negative coccobacillus causing kennel cough in dogs. On occasion it causes upper and lower respiratory infection in humans, principally HIV-infected patients. Infection has been associated with contact with dogs and cats, suggesting animal-to-human transmission. Treatment of *B bronchiseptica* infection is guided by results of in vitro susceptibility tests.

MENINGOCOCCAL MENINGITIS



ESSENTIALS OF DIAGNOSIS

- ▶ Fever, headache, vomiting, delirium, convulsions.
- ▶ Petechial rash on skin and mucous membranes in many.
- ▶ Neck and back stiffness and positive Kernig and Brudzinski signs are characteristic.
- ▶ Purulent spinal fluid with gram-negative intracellular and extracellular diplococci.
- ▶ Culture of cerebrospinal fluid, blood, or petechial aspiration confirms the diagnosis.

► General Considerations

Meningococcal meningitis is caused by *Neisseria meningitidis* of groups A, B, C, Y, and W-135, among others. Meningitis due to serogroup A is uncommon in the United States. Serogroup B generally causes sporadic cases. Serogroup C meningococcus is the most common cause of epidemic disease in the United States. Up to 40% of persons are nasopharyngeal carriers of meningococci, but disease develops in relatively few of these persons. Infection is transmitted by droplets. The clinical illness may take the form of meningococcemia (a fulminant form of septicemia without meningitis), meningococcemia with meningitis, or meningitis. Recurrent meningococcemia with fever, rash, and arthritis is seen rarely in patients with certain terminal complement deficiencies. Asplenic patients are also at risk.

► Clinical Findings

A. Symptoms and Signs

High fever, chills, nausea, vomiting, and headache as well as back, abdominal, and extremity pains are typical. Rapidly developing confusion, delirium, seizures, and coma occur in some. On examination, nuchal and back rigidity are typical. Positive Kernig and Brudzinski signs (Kernig sign is pain in the hamstrings upon extension of the knee with the hip at 90-degree flexion; Brudzinski sign is flexion of the knee in response to flexion of the neck) are specific but not sensitive findings. A petechial rash appearing all over the body, including on mucous membranes, on the lower extremities, and at pressure points, is found in most cases. Petechiae may vary in size from pinpoint lesions to large ecchymoses or even skin gangrene that may later slough.

B. Laboratory Findings

Lumbar puncture typically reveals a cloudy or purulent cerebrospinal fluid, with elevated pressure, increased protein, and decreased glucose content. The fluid usually contains greater than 1000 cells/mcL ($1.0 \times 10^9/L$) with polymorphonuclear cells predominating and containing gram-negative intracellular diplococci. The organism is

usually demonstrated by smear and culture of the cerebrospinal fluid, oropharynx, blood, or aspirated petechiae. The absence of organisms in a Gram-stained smear of the cerebrospinal fluid sediment does not rule out the diagnosis. The capsular polysaccharide can be demonstrated in cerebrospinal fluid or urine by latex agglutination; this is useful in partially treated patients, though sensitivity is 60–80%.

Disseminated intravascular coagulation is an important complication of meningococcal infection and is typically present in toxic patients with ecchymotic skin lesions.

► Differential Diagnosis

Meningococcal meningitis must be differentiated from other meningitides. In small infants and in older adults, fever or stiff neck is often missing, and altered mental status may dominate the picture.

Rickettsial, echovirus, and, rarely, other bacterial infections (eg, staphylococcal infections, scarlet fever) also cause petechial rash.

► Prevention

Four meningococcal vaccines are available. There are two vaccines with coverage against meningococcal serogroups A, C, Y, and W-135 and two with coverage against meningococcal serogroup B. The two vaccines effective for meningococcal serogroups A, C, Y, and W-135 are the meningococcal polysaccharide vaccine (MPSV4), indicated for vaccination of persons over age 55, and the conjugate vaccine (MCV4), indicated for persons aged 2–55 years. The two vaccines against meningococcal serogroup B are MenB-FHbp and MenB-4C; they are approved for persons aged 10–25 years and are not interchangeable.

The Advisory Committee on Immunization Practices recommends immunization with a dose of MCV4 for preadolescents aged 11–12 with a booster at age 16 (see www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html). For ease of program implementation, persons aged 21 years or younger should have documentation of receipt of a dose of MCV4 not more than 5 years before enrollment to college. If the primary dose was administered before the sixteenth birthday, a booster dose should be administered before enrollment. Vaccine is also recommended as a two-dose primary series administered 2 months apart for persons aged 2 through 54 years with persistent complement deficiency, persons with functional or anatomic asplenia, and for adolescents with HIV infection. All other persons at increased risk for meningococcal disease (eg, military recruits, microbiologists routinely exposed to isolates of *N meningitidis*, or travelers to an epidemic or highly endemic country) should receive a single dose. One of the meningococcal serogroup B vaccines may be administered to persons 10 years of age or older who are at increased risk for meningococcal disease. These persons include those with persistent complement deficiencies; persons with anatomic or functional asplenia; microbiologists; and persons identified to be at increased risk because of a serogroup B meningococcal disease outbreak. Vaccination of persons aged 16–23 years may provide short-term protection against most strains of serogroup B meningococcal disease.

Eliminating nasopharyngeal carriage of meningococci is an effective prevention strategy in closed populations and to prevent secondary cases in household or otherwise close contacts. Rifampin, 600 mg orally twice a day for 2 days, ciprofloxacin, 500 mg orally once, or one intramuscular 250-mg dose of ceftriaxone is effective. Cases of fluoroquinolone-resistant meningococcal infections have been identified in the United States. However, ciprofloxacin remains a recommended empiric agent for eradication of nasopharyngeal carriage. School and work contacts ordinarily need not be treated. Hospital contacts receive therapy only if intense exposure has occurred (eg, mouth-to-mouth resuscitation). Accidentally discovered carriers without known close contact with meningococcal disease do not require prophylactic antimicrobials.

► Treatment

Blood cultures must be obtained and intravenous antimicrobial therapy started immediately. This may be done prior to lumbar puncture in patients in whom the diagnosis is not straightforward and for those in whom MR or CT imaging is indicated to exclude mass lesions. Aqueous penicillin G is the antibiotic of choice (24 million units/24 h intravenously in divided doses every 4 hours). The prevalence of strains of *N meningitidis* with intermediate resistance to penicillin in vitro (MICs 0.1–1 mcg/mL) is increasing, particularly in Europe. Penicillin-intermediate strains thus far remain fully susceptible to ceftriaxone and other third-generation cephalosporins used to treat meningitis, and these should be effective alternatives to penicillin. In penicillin-allergic patients or those in whom *Haemophilus influenzae* or gram-negative meningitis is a consideration, ceftriaxone, 2 g intravenously every 12 hours, should be used. Treatment should be continued in full doses by the intravenous route until the patient is afebrile for 5 days. Shorter courses—as few as 4 days if ceftriaxone is used—are also effective.

► When to Admit

All patients with suspected meningococcal infection should be admitted for evaluation and empiric intravenous antibiotic therapy.

Linder KA et al. JAMA patient page. Meningococcal meningitis. JAMA. 2019;321:1014. [PMID: 30860561]

MacNeil JR et al. Use of serogroup B meningococcal vaccines in adolescents and young adults: recommendations of the Advisory Committee on Immunization Practices, 2015. MMWR Morb Mortal Wkly Rep. 2015;64:1171. [PMID: 26492381]

INFECTIONS CAUSED BY HAEMOPHILUS SPECIES

H influenzae and other *Haemophilus* species may cause sinusitis, otitis, bronchitis, epiglottitis, pneumonia, cellulitis, arthritis, meningitis, and endocarditis. Nontypeable strains are responsible for most disease in adults. Alcohol use disorder, smoking, chronic lung disease, advanced age, and HIV infection are risk factors. *Haemophilus* species colonize the upper respiratory tract in patients with chronic

obstructive pulmonary disease and frequently cause purulent bronchitis.

Beta-lactamase-producing strains are less common in adults than in children. For adults with sinusitis, otitis, or respiratory tract infection, oral amoxicillin, 750 mg twice daily for 10–14 days, is adequate. For beta-lactamase-producing strains, use of the oral fixed-drug combination of amoxicillin, 875 mg, with clavulanate, 125 mg, is indicated. For the penicillin-allergic patient, oral cefuroxime axetil, 250 mg twice daily; or a fluoroquinolone (ciprofloxacin, 500 mg orally twice daily; levofloxacin, 500–750 mg orally once daily; or moxifloxacin, 400 mg orally once daily) for 7 days is effective. Azithromycin, 500 mg orally once followed by 250 mg daily for 4 days, is preferred over clarithromycin when a macrolide is the preferred agent. Trimethoprim-sulfamethoxazole (160/800 mg orally twice daily) can be considered, but resistance rates have been reported to be up to 25%.

In the more seriously ill patient (eg, the toxic patient with multilobar pneumonia), ceftriaxone, 1 g/day intravenously, is recommended pending determination of whether the infecting strain produces beta-lactamase. A fluoroquinolone (see above for dosages) can be used for the penicillin-allergic patients for a 10- to 14-day course of therapy.

Epiglottitis is characterized by an abrupt onset of high fever, drooling, and inability to handle secretions. An important clue to the diagnosis is complaint of a severe sore throat despite an unimpressive examination of the pharynx. Stridor and respiratory distress result from laryngeal obstruction. The diagnosis is best made by direct visualization of the cherry-red, swollen epiglottis at laryngoscopy. Because laryngoscopy may provoke laryngospasm and obstruction, especially in children, it should be performed in an intensive care unit or similar setting, and only at a time when intubation can be performed promptly. Ceftriaxone, 1 g intravenously every 24 hours for 7–10 days, is the drug of choice. Trimethoprim-sulfamethoxazole or a fluoroquinolone (see above for dosage) may be used in the patient with serious penicillin allergy.

Meningitis, rare in adults, is a consideration in the patient who has meningitis associated with sinusitis or otitis. Initial therapy for suspected *H influenzae* meningitis should be with ceftriaxone, 4 g/day in two divided doses, until the strain is proved not to produce beta-lactamase. Meningitis is treated for at least 7 days. Dexamethasone, 0.15 mg/kg intravenously every 6 hours, may reduce the incidence of long-term sequelae, principally hearing loss.

Brouwer MC et al. Epidemiology of community-acquired bacterial meningitis. *Curr Opin Infect Dis*. 2018;31:78. [PMID: 29176349]

Sriram KB et al. Nontypeable *Haemophilus influenzae* and chronic obstructive pulmonary disease: a review for clinicians. *Crit Rev Microbiol*. 2018;44:125. [PMID: 28539074]

INFECTIONS CAUSED BY MORAXELLA CATARRHALIS

M catarrhalis is a gram-negative aerobic coccus morphologically and biochemically similar to *Neisseria*. It causes sinusitis, bronchitis, and pneumonia. Bacteremia and

meningitis have also been reported in immunocompromised patients. The organism frequently colonizes the respiratory tract, making differentiation of colonization from infection difficult. If *M catarrhalis* is the predominant isolate, therapy is directed against it. *M catarrhalis* typically produces beta-lactamase and therefore is usually resistant to ampicillin and amoxicillin. It is susceptible to amoxicillin-clavulanate, ampicillin-sulbactam, trimethoprim-sulfamethoxazole, ciprofloxacin, and second- and third-generation cephalosporins.

LEGIONNAIRES DISEASE

ESSENTIALS OF DIAGNOSIS

- ▶ Patients are often immunocompromised, smoke cigarettes, or have chronic lung disease.
- ▶ Scant sputum production, pleuritic chest pain, toxic appearance.
- ▶ Chest radiograph: focal patchy infiltrates or consolidation.
- ▶ Gram stain of sputum: polymorphonuclear leukocytes and no organisms.

General Considerations

Legionella infection ranks among the three or four most common causes of community-acquired pneumonia and is considered whenever the etiology of a pneumonia is in question. Legionnaires disease is more common in persons who smoke cigarettes and in those with chronic lung disease or who are immunocompromised. Outbreaks have been associated with contaminated water sources, such as showerheads and faucets in patient rooms and air conditioning cooling towers.

Clinical Findings

A. Symptoms and Signs

Legionnaires disease is one of the atypical pneumonias, so called because a Gram-stained smear of sputum does not show organisms. However, many features of Legionnaires disease are more like typical pneumonia, with high fevers, toxic appearance, pleurisy, and grossly purulent sputum. Nausea, vomiting, and diarrhea may be prominent. There may be relative bradycardia. Classically, this pneumonia is caused by *Legionella pneumophila*, though other species can cause identical disease.

B. Laboratory Findings

There may be hyponatremia, hypophosphatemia, elevated liver enzymes, and elevated creatine kinase. Culture of *Legionella* species has a 80–90% sensitivity. Dieterle silver staining of tissue, pleural fluid, or other infected material is also a reliable method for detecting *Legionella* species. Direct fluorescent antibody stains and serologic testing such as urinary antigen are less sensitive because these will