



## BASIC INFORMATION

### DEFINITION

There are two forms of heparin-induced thrombocytopenia (HIT). Type 1 HIT is a mild, transient decrease in platelet count that occurs during the first few days of heparin exposure due to platelet agglutination. This form is benign, and the platelet count will return to normal while heparin is continued. This section will refer to Type 2 HIT, an antibody-mediated thrombocytopenia that is associated with a high risk of developing thrombosis.

### SYNOMYS

Type II heparin-induced thrombocytopenia  
Heparin-induced thrombocytopenia and thrombosis (HITT)  
White clot syndrome  
Heparin-associated immune thrombocytopenia

### ICD-9CM CODES

289.84 Heparin-induced thrombocytopenia (HIT)

### ICD-10CM CODES

D75.82 Heparin-induced thrombocytopenia (HIT)

### EPIDEMIOLOGY & DEMOGRAPHICS

**INCIDENCE:** Occurs in 0.2% to 5% of patients exposed to heparin. Unfractionated heparin is associated with a 5 to 10 times higher risk of HIT compared with low-molecular-weight heparin. Initially, there was an overwhelming underdiagnosis of HIT; however, since the introduction of HIT antibody ELISA test, there is a propensity to over-diagnose HIT irrespective of the clinical scenario.

**PREDOMINANT SEX AND AGE:** Females are at slightly higher risk than males. More common in adults but may also occur in children.

**RISK FACTORS:** Longer duration of exposure to heparin, type of heparin (unfractionated heparin has a greater risk), type of patient (surgical patients, especially cardiac and orthopedic surgery, are at higher risk than medical patients).

### PHYSICAL FINDINGS & CLINICAL PRESENTATION

Suspect in a patient with:

- Exposure to heparin for 4 to 14 days OR who was exposed to heparin in the prior 3 mo.
- Unexplained platelet count decrease to 50% below pretreatment baseline.
- Onset of thrombocytopenia 5 to 10 days after heparin initiation.
- Evidence of acute venous or arterial thrombosis.
- Skin lesions/necrosis at heparin injection sites.
- Acute anaphylactoid reaction during administration of heparin bolus.

### ETOLOGY

Occurs due to the formation of IgG antibodies, directed against heparin in complex with platelet factor 4, which bind to and activate platelets.

Activated platelets release platelet factor 4 (leading to more antibody production) and undergo aggregation and premature removal from the circulation (resulting in thrombocytopenia). This platelet activation and antibody formation also can lead to thrombosis. Fig. EH1-27 illustrates the mechanism of HIT.

- Drug-induced thrombocytopenia (other than heparin).
- Antiphospholipid antibody syndrome.

### WORKUP

HIT is first and foremost a clinical diagnosis that is confirmed with laboratory testing. See Table H1-13 for workup based on pretest probability. If the patient has a low pretest probability score, heparin can be safely continued, and there is no need to send for further testing for HIT. If the patient has a moderate to high pretest probability, HIT testing (Table H1-14), imaging studies for lower-extremity deep venous thrombosis (also consider imaging of upper extremities if swelling is present or venous catheters are in place), cessation of heparin products, and alternative anticoagulation should all be performed.

**TABLE H1-13 A Diagnostic and Treatment Approach to Heparin-Induced Thrombocytopenia**

Suspicion of HIT Based upon the "4 T's"	Score	Pre-Test Probability Score Criteria		
		2	1	0
Thrombocytopenia	<input type="checkbox"/>	nadir 20-100, or >50% platelet fall	nadir 10-19, or 30-50% platelet fall	nadir <10, or <30% platelet fall
Timing of onset of platelet fall	<input type="checkbox"/>	day 5-10, or ≤ day 1 with recent heparin*	>day 10 or failing unclear (but fits with HIT)	≤ day 1 (no recent heparin)
Thrombosis or other sequelae	<input type="checkbox"/>	proven thrombosis, skin necrosis, or ASR†	progressive, recurrent, or silent thrombosis; erythematous skin lesions possible	none
Other cause of platelet fall	<input type="checkbox"/>	none evident		definite
Total Pre-Test Probability Score	<input type="checkbox"/>	periodic reassessment as new information can change pre-test probability (e.g., positive blood cultures)		
		Total Pre-Test Probability Score		
		High	Moderate	Low
		8   7   6	5   4	3   2   1   1   0
Stop heparin‡, give alternative non-heparin anticoagulant argatroban§ or lepirudin# or danaparoid** (or bivalirudin†† or fondaparinux†††)		Physician judgment		Continue (LMW) heparin
<b>Positive test for HIT antibodies</b> ← <b>HIT Test</b> → <b>Negative test for HIT antibodies</b> Continue non-heparin anticoagulant until platelet count recovery <b>Thrombosis***</b> ← <b>Imaging studies for lower-limb DVT†††††</b> → <b>No Thrombosis</b> If HIT, continue non-heparin anti-coagulant until platelet count recovery, then cautious coumarin overlap¶¶¶ <b>Recent heparin indicates exposure within the past 30 days (2 points) or past 30-100 days (1 point)</b> †ASR, acute systemic reaction following i.v. heparin bolus ‡stop all heparin, including catheter "flushes" and, possibly, heparin-coated catheters §argatroban: approved (U.S., Canada) for isolated HIT and HIT complicated by thrombosis (2 µg/kg/min i.v., adjusted to 1.5-3.0X patient's baseline aPTT or the mean of the laboratory normal range); reduce dose for hepatobiliary compromise: may increase INR more than the other direct thrombin inhibitors, thus requiring care in managing coumarin overlap (see ¶¶¶ below) #lepirudin: approved (U.S., Canada, E.U., elsewhere) for treatment of thrombosis complicating HIT ( $\pm$ 0.4 mg/kg i.v. bolus, then 0.15 mg/kg/h adjusted to 1.5-2.5X patient's baseline aPTT or mean of the laboratory normal range); used (off-label) also to treat isolated HIT (0.1 mg/kg/h, adjusted by aPTT); to avoid overdosing and anaphylaxis, it may be preferable to omit the bolus, and begin as i.v. infusion (except when facing life- or limb-threatening thrombosis); reduce dose for renal insufficiency **danaparoid: usual i.v. bolus, 2250 U (body weight 60-75 kg) followed by infusion (400 U/hr for 4 h, then 300 U/h for 4 h, then 200 U/h, adjusted by anti-factor Xa levels); this therapeutic-dose regimen is appropriate both for isolated HIT and for HIT complicated by thrombosis (though higher than approved dose in some jurisdictions); withdrawn from U.S. market (2002) ††bivalirudin: no bolus, i.v. infusion 0.15 mg/kg/h adjusted by aPTT; limited experience (off-label) †††fondaparinux: dosing for HIT not established; limited experience (off-label) ¶¶¶delay coumarin pending substantial platelet count recovery (at least >100, preferably >150); begin coumarin in low doses, with at least 4-5 day overlap, stopping alternative anticoagulant when INR therapeutic for 2 days and platelets recovered §§depending on physician confidence in the laboratory's ability to rule out HIT antibodies (usually, negative PF4-dependent enzyme-immunoassay and/or washed platelet activation assay performed by an experienced laboratory) ***some thrombi may require special treatment, e.g., thrombectomy for large limb artery thrombosis †††routine ultrasound of lower-limb veins recommended, since many HIT patients have subclinical deep-vein thrombosis (DVT)				

From Warkentin TE.; et al. Platelet-endothelial interactions: sepsis, HIT, and antiphospholipid syndrome. *Hematology (Am Soc Hematol Educ Prog)* 497-519, 2003.

**TABLE H1-14** Laboratory Assays for Heparin-Induced Thrombocytopenia

Assay	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Functional assay (e.g., serotonin release assay)	88	~100	~100	81
PF4/heparin enzyme immunoassay (ELISA)	95-98	86	93	95

ELISA, Enzyme-linked immunosorbent assay; PF4, platelet factor 4.

From Goldman L, Schafer Al: *Goldman's Cecil medicine*, ed 24, Philadelphia, 2012, Saunders.

Patients with intermediate and high pretest probability but no HIT antibodies or intermediate pretest probability and only weakly positive HIT antibodies (based on optical density, see below) can resume heparin use as HIT is unlikely in these scenarios. Patients with high pretest probability and weakly positive antibodies or intermediate/high pretest probability and moderate to strongly positive antibodies likely have HIT and should be treated as such.

### LABORATORY TESTS

These can be broadly divided into immunoassays (high sensitivity) and functional assays (high specificity). In the appropriate clinical setting, testing for HIT antibodies with an enzyme-linked immunosorbent assay, or ELISA, can be useful. This test is very sensitive, but not specific. The majority of patients with positive testing for HIT antibodies will not develop clinical HIT. Thus, HIT antibody testing is more effective for ruling out rather than confirming the diagnosis of HIT. More recently, use of the HIT antibody optical density as well as the immunoglobulin subtypes of the HIT antibody have entered the diagnostic realm. Higher optical density levels are associated with increased likelihood of a positive functional assay, higher pretest probability score, and increased risk of thrombosis. Weakly positive optical densities (0.4 to 1.0) are only rarely associated with functional assay positivity. In contrast, optical densities >2.0 almost always show heparin-dependent platelet activation. Optical densities are thus defined as weakly positive (0.4-1.0), moderately positive (1.0-2.0), or strongly positive (>2.0). The HIT antibody IgG subtype is the pathologic antibody for HIT. Hence, use of IgG-specific ELISA kits increases the test specificity over the polyclonal (IgA/M/G) antibody. Patients with low pretest probability should not have HIT antibody testing performed, while all patients with intermediate and high pretest probability of HIT benefit from HIT antibody testing.

The gold standard test for HIT is to measure heparin-dependent platelet activation via the functional serotonin release assay (14C-SRA). This is both a highly sensitive and specific test. Donor platelets are incubated with radiolabeled serotonin. The platelets internalize the serotonin and are then exposed to the patient's serum and heparin at a therapeutic concentration. If antibodies to the platelet factor 4-heparin complex are present in the patient's serum, the platelets react and released radioactive serotonin is then measured. Availability and turn-around time of this test is dependent on the institution, which can influence the test's clinical utility. Cases where there is intermediate pretest probability, but only a weakly positive HIT antibody score, benefit the most from confirmatory SRA testing. Here, a positive SRA test will argue for HIT while negative SRA tests will suggest absence of HIT.

### IMAGING STUDIES

Doppler sonography of the extremities in the correct clinical setting.

### RX TREATMENT

- For patients with a moderate or high pretest probability, discontinue all heparin exposure. Even if the patient does not have a clinically evident thrombosis, he or she is at a 50% risk of developing a clot within the subsequent 30 days. Thus, the patient must be started on an alternate anticoagulant.
- Three agents, all direct thrombin inhibitors, are approved for this indication:
  - Argatroban (avoid in liver dysfunction).
  - Lepirudin (avoid in renal dysfunction).
  - Bivalirudin (bivalirudin is approved only for patients with HIT or at risk of HIT who are undergoing PCI).
- These drugs should be continued as a single agent until the platelet count returns to baseline (generally a platelet count of  $150 \times 10^9/L$ ) but it is important to consider the individual

patient's baseline), then warfarin can be added at a maximum dose of 5 mg/day. This overlap therapy should continue until the platelet count has reached a stable plateau, the INR has reached the intended target (remember that argatroban artificially elevates the INR), and after a minimum overlap of 5 days of both the direct thrombin inhibitor and warfarin. The length of treatment is controversial, but most clinicians agree that 1 month of alternate anticoagulation is sufficient in the absence of thrombosis, while 3 to 6 months of treatment are required in the presence of thrombosis.

- There are emerging data showing efficacy and lower bleeding risk in HIT for fondaparinux when compared with the direct thrombin inhibitors. Fondaparinux is a synthetic pentasaccharide that binds antithrombin, causing long-acting inhibition of activated factor X, but not thrombin. It is not FDA approved for HIT, but its use in HIT in pregnancy has been reported. It can initiate the formation of anti-PF4 antibodies, but it does not support platelet activation by the newly formed immune complexes.

### NONPHARMACOLOGIC THERAPY

All nonpharmacologic therapies including surgical procedures.

### REFERRAL

Request a hematology consultation.

### PEARLS & CONSIDERATIONS

#### COMMENTS

HIT paradoxically causes thrombocytopenia and *clotting*, not bleeding.

#### PREVENTION

Consider the use of low-molecular-weight heparin (as opposed to unfractionated heparin) as DVT prophylaxis.

### EBM EVIDENCE

Available at [www.expertconsult.com](http://www.expertconsult.com)

### SUGGESTED READINGS

Available at [www.expertconsult.com](http://www.expertconsult.com)

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## EBM EVIDENCE

### Abstract<sup>[1]</sup>

#### Background:

Some patients with acute VTE who may previously have been exposed to heparin products have unrecognized antibodies implicated in heparin-induced thrombocytopenia (HIT). Antibody prevalence and patient consequences upon exposure to heparin, low-molecular-weight heparin, and fondaparinux are uncertain.

#### Methods:

In this secondary analysis, we tested patients in the MATISSE VTE studies at study entry for heparin-dependent antibodies and further tested patients with enzyme-linked immunosorbent assay (ELISA)-positive results for platelet-activating antibodies. We compared the risk of HIT (>50% fall in platelet count, heparin-dependent antibodies, no contradicting features) between patients treated with heparin (either unfractionated or low molecular weight [enoxaparin]) vs those who received fondaparinux. Comparison groups for thrombocytopenia occurrence comprised patients with ELISA-positive, platelet-activating, antibody-positive results; ELISA-positive, but platelet-activating antibody-negative results; and randomly selected antibody-negative results.

#### Results:

A total of 127 of 3994 patients (3.2%) had ELISA-positive results at baseline, but only 14 (0.4%; 95% CI, 0.2%-0.6%) had platelet-activating antibodies. Among these 14, four treated with unfractionated or low-molecular-weight heparin developed HIT compared with zero of 10 fondaparinux-treated patients (OR, 95; 95% CI, 8-1,123;  $P<.001$ ). This frequency (four of four, 100%) significantly differed from that of both heparin-treated patients whose results were ELISA positive, but platelet-activating antibody negative, and from heparin-treated antibody-negative control subjects (zero of 15 and zero of 27, respectively;  $P<.001$  for both).

#### Conclusions:

Of patients with VTE, 0.4% had pathologic platelet-activating heparin-dependent antibodies rather than the 3.2% detected by the recommended cutoff of the commercial ELISA. Among study patients with acute VTE who had platelet-activating antibodies, treatment with fondaparinux reduced the risk of precipitating rapid-onset HIT. **A**

### Evidence-Based Reference

Warkentin TE, et al.: Prevalence and risk of preexisting heparin-induced thrombocytopenia antibodies in patients with acute VTE, *Chest* 140:366-373, 2011. **A**

## SUGGESTED READINGS

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Kelton JK et al.: Nonheparin anticoagulants for heparin-induced thrombocytopenia, *N Engl J Med* 368:737-744, 2013.

Linkins LA et al.: Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, *Chest* 141(2 suppl):e495S-e530S, 2012.

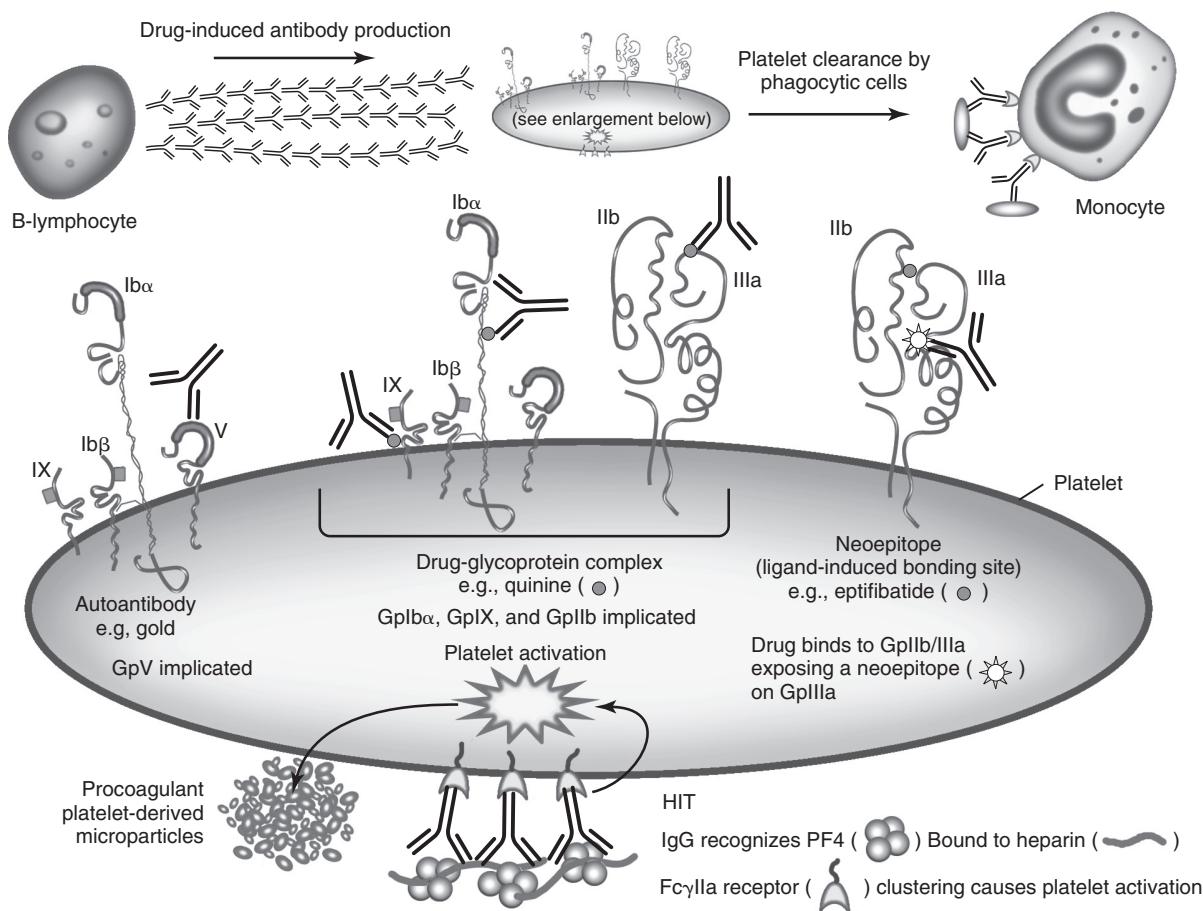
Warkentin TE et al.: Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition), *Chest* 133:340-380, 2008.

Warkentin TE et al.: Platelet-endothelial interactions: sepsis, HIT, and antiphospholipid syndrome, *Hematology (Am Soc Hematol Educ Prog)* 497-519, 2003.

Warkentin TE et al.: The serological profile of fondaparinux-associated heparin-induced thrombocytopenia syndrome, *Thromb Haemost* 108:394-396, 2012.

# Heparin-Induced Thrombocytopenia

595.e2



**FIGURE EH1-27 Mechanisms of drug-induced immune thrombocytopenia.** Four immune thrombocytopenic syndromes are illustrated. On the *bottom* of the schematic platelet, heparin-induced thrombocytopenia (HIT) is illustrated, indicating that IgG antibodies bind to complexes of platelet factor 4 (PF4) and heparin, with the Fc regions of the antibodies binding to the platelet Fc $\gamma$ llla receptors, resulting in platelet activation (including generation of procoagulant, platelet-derived microparticles). On the *top* of the schematic platelet, three mechanisms are illustrated that lead to increased platelet clearance by phagocytic cells. From *left to right*, these are autoantibody-induced immune thrombocytopenia (e.g., gold-induced antiglycoprotein V [GPV] antibodies); drug-dependent antibodies reactive against drug (or drug metabolite)/platelet glycoprotein complex(es) (e.g., quinine-induced thrombocytopenia, in which drug-dependent antibodies against GPIb $\alpha$ , GPIX, and GPIb have been implicated, resulting in an antibody/drug/glycoprotein ternary complex); and antibodies against neoepitope(s) formed in the presence of a drug (e.g., eptifibatide-induced immune thrombocytopenia caused by formation of ligand-induced binding site elsewhere on the GPIb/IIIa complex following eptifibatide binding). Note that preexisting (naturally occurring) antibodies can explain abrupt-onset thrombocytopenia in a patient receiving eptifibatide for the first time. (From Hoffman R et al: *Hematology, basic principles and practice*, ed 5, Philadelphia, 2009, Churchill Livingstone.)



## BASIC INFORMATION

### DEFINITION

Hepatic encephalopathy is a neuropsychiatric syndrome occurring in patients with severe impairment of liver function and consequent accumulation of toxic products not metabolized by the liver. It is characterized by gradual impairment of the ability to perform mental tasks and to react to external stimuli.

**Minimal hepatic encephalopathy** refers to patients with hepatic cirrhosis and mild cognitive impairment, but no history of overt encephalopathy.

### SYNOMYS

Hepatic coma

#### ICD-9CM CODES

572.2 Hepatic encephalopathy

#### ICD-10CM CODES

K72.0 Acute and subacute hepatic failure

K72.1 Chronic hepatic failure

K72.9 Hepatic failure, unspecified

### EPIDEMIOLOGY & DEMOGRAPHICS

**INCIDENCE/PREVALENCE:** Hepatic encephalopathy occurs in >40% of all cases of cirrhosis.

### PHYSICAL FINDINGS & CLINICAL PRESENTATION

Hepatic encephalopathy can be classified by clinical stages described in **Table H1-15**.

The physical examination in hepatic encephalopathy varies with the stage and may reveal the following abnormalities:

- Skin: jaundice, palmar erythema, spider angiomas, ecchymosis, dilated superficial periumbilical veins (*caput medusae*) in patients with cirrhosis.
- Eyes: scleral icterus, Kayser-Fleischer rings (Wilson's disease).
- Breath: fetor hepaticus.
- Chest: gynecomastia in men with chronic liver disease.
- Abdomen: ascites, small nodular liver (cirrhosis), tender hepatomegaly (congestive hepatomegaly).

- Rectal examination: hemorrhoids (portal hypertension), guaiac-positive stool (alcoholic gastritis, bleeding esophageal varices, peptic ulcer disease, bleeding hemorrhoids).
- Genitalia: testicular atrophy in males with chronic liver disease.
- Extremities: pedal edema from hypoalbuminemia.
- Neurologic: flapping tremor (asterixis), obtundation, coma with or without decerebrate posturing.

### ETIOLOGY

- Hepatic encephalopathy is thought to be caused mainly by accumulation of unmetabolized ammonia.
- Precipitating factors in patients with underlying cirrhosis (upper gastrointestinal bleeding, hypokalemia, hypomagnesemia, analgesic and sedative drugs, sepsis, alkalinosis, increased dietary protein).
  - Acute fulminant viral hepatitis.
  - Drugs and toxins (e.g., isoniazid, acetaminophen, diclofenac and other NSAIDs, statins, methyldopa, loratadine, propylthiouracil, lisinopril, labetalol, halothane, carbon tetrachloride, erythromycin, nitrofurantoin, troglitazone, herbal products, flavocoxid).
  - Reye's syndrome.
  - Shock and/or sepsis.
  - Fatty liver of pregnancy.
  - Metastatic carcinoma, hepatocellular carcinoma.
  - Other: autoimmune hepatitis, ischemic veno-occlusive disease, sclerosing cholangitis, heat stroke, amebic abscesses.

## Dx DIAGNOSIS

### DIFFERENTIAL DIAGNOSIS

- Delirium caused by medications or illicit drugs.
- Cerebrovascular accident, subdural hematoma.
- Meningitis, encephalitis.
- Hypoglycemia.
- Uremia.
- Cerebral anoxia.
- Hypercalcemia.
- Metastatic neoplasm to brain.
- Alcohol withdrawal syndrome.

### WORKUP

Hepatic encephalopathy should be considered in any patient with cirrhosis who presents with neuropsychiatric manifestations. Exclude other etiologies with comprehensive history (obtained from patient, relatives, and others), physical examination, and laboratory and imaging studies. A pertinent history should include exposure to hepatitis, ethanol intake, drug history, exposure to toxins, IV drug abuse, measles or influenza with aspirin use (Reye's syndrome), and history of carcinoma (primary or metastatic). Minimal hepatic encephalopathy may not be obvious on clinical examination, but can be detected with neurophysiologic and neuropsychiatric testing.

### LABORATORY TESTS

- Alanine aminotransferase, aspartate aminotransferase, bilirubin, alkaline phosphatase, glucose, calcium, electrolytes, blood urea nitrogen, creatinine, albumin.
- Complete blood count, platelet count, prothrombin time, partial thromboplastin time.
- Serum and urine toxicology screen in suspected medication or illegal drug use.
- Blood and urine cultures, urinalysis.
- Venous ammonia level. Measurement of serum ammonia level is useful in the evaluation of acute liver failure because levels correlate with the severity of encephalopathy and elevated levels are predictive of severe encephalopathy and cerebral edema. It is not useful for the evaluation or screening of hepatic encephalopathy in patients with chronic liver disease because it can neither rule in nor rule out hepatic encephalopathy, and levels do not correlate with the degree of encephalopathy.
- Arterial blood gases.

### IMAGING STUDIES

CT scan or MRI of the brain may be useful in selected patients to exclude other etiologies when diagnosis is unclear.

## Rx TREATMENT

### NONPHARMACOLOGIC THERAPY

- Identification and treatment of precipitating factors.
- Restriction of protein intake (30 to 40 g/day) to reduce toxic protein metabolites.

### ACUTE GENERAL Rx

**Table H1-16** summarizes the management of fulminant hepatic failure.

#### Reduction of colonic ammonia production:

- Lactulose 30 ml of 50% solution qid initially; dose is subsequently adjusted depending on clinical response. Ornithine aspartate 9 g tid is also effective. Lactulose may improve hepatic encephalopathy but may be less effective than antibiotics.
- Neomycin 1 g PO q4 to 6h or given as a 1% retention enema solution (1 g in 100 ml of isotonic saline solution); neomycin should be used with caution in patients with renal

**TABLE H1-15** Clinical Stages of Hepatic Encephalopathy

Stage	Asterixis	EEG Changes	Clinical Manifestations
I (prodrome)	Slight	Minimal	Mild intellectual impairment, disturbed sleep-wake cycle
II (impending)	Easily elicited	Usually generalized	Drowsiness, confusion, coma/inappropriate behavior, disorientation, mood swings
III (stupor)	Present if patient cooperative	Grossly abnormal slowing of rhythm	Drowsy, unresponsive to verbal commands, markedly confused, delirious, hyperreflexia, positive Babinski sign
IV (coma)	Usually absent	Appearance of delta waves, decreased amplitudes	Unconscious, decerebrate or decorticate response to pain present (stage IVa) or absent (stage IVb)

EEG, Electroencephalogram.

From Fuhrman BP et al: *Pediatric critical care*, ed 4, Philadelphia, 2011, Saunders.

**TABLE H1-16** Management of Fulminant Hepatic Failure

No sedation except for procedures
Minimal handling
Enteric precautions until infection ruled out
Monitor:
• Heart and respiratory rate
• Arterial BP, CVP
• Core/toe temperature
• Neurologic observations
• Gastric pH (>5.0)
• Blood glucose (>4 mmol/L)
• Acid-base
• Electrolytes
• PT, PTT
Fluid balance
• 75% maintenance
• Dextrose 10%–50% (provide 6–10 mg/kg/min)
• Sodium (0.5–1 mmol/L)
• Potassium (2–4 mmol/L)
Maintain circulating volume with colloid/FFP
Coagulation support only if required
Drugs
• Vitamin K
• H <sub>2</sub> antagonist
• Antacids
• Lactulose
• N-acetylcysteine for acetaminophen toxicity
• Broad-spectrum antibiotics
• Antifungals
Nutrition
• Enteral feeding (1–2 g protein/kg/day)
• PN if ventilated

BP, Blood pressure; CVP, central venous pressure; FFP, fresh frozen plasma; PN, parenteral nutrition; PT, prothrombin time; PTT, partial thromboplastin time.

From Fuhrman BP et al: *Pediatric critical care*, ed 4, Philadelphia, 2011, Saunders.

#### BOX H1-4 Various Prognostic Criteria Used for Liver Transplantation in Patients with Fulminant Hepatic Failure

##### King's College Criteria

Acetaminophen overdose:

- Arterial pH <7.3 (irrespective of grade of encephalopathy) or
- PT >100 sec (INR >6.5)
- Serum creatinine >3.4 mg/dl (>300 μmol/L)
- Patients with grade III and IV hepatic encephalopathy

Nonacetaminophen liver injury:

- PT >100 sec (INR >6.5) (irrespective of grade of encephalopathy) or any three of the following variables:
  1. Age <10 or >40 years
  2. Non-A, non-B hepatitis, halothane hepatitis, idiosyncratic drug reactions
  3. Jaundice >7 days before onset of encephalopathy
  4. Serum bilirubin 17.4 mg/dl (300 μmol/L)
  5. PT >50 sec

##### Cliché Criteria

Factor V <20% in persons <30 years or both of the following:

- Factor V <30% in patients >30 years
- Grade III or IV encephalopathy

##### Serum Gc Globulin Levels

- Decreasing Gc levels due to dying hepatocytes

##### Serum α-Fetoprotein Level

- Serial increase from day 1 to day 3 has shown correlation with survival

##### Liver Biopsy<sup>32</sup>

70% necrosis is discriminant of 90% mortality

insufficiency. Metronidazole 250 mg qid may be as effective as neomycin and is not nephrotoxic; however, long-term use can be associated with neurotoxicity.

- A combination of lactulose and neomycin can be used when either agent is ineffective alone.
- The oral antibiotic rifaximin (550 mg PO bid) is effective in reducing the risk of recurrent hepatic encephalopathy in patients with cirrhosis. It can be taken with lactulose, and the combination of lactulose and rifaximin is superior to lactulose alone in reversing hepatic encephalopathy. Rifamixin has also been shown to be effective in improving psychometric performance and health-related quality of life in patients with minimal hepatic encephalopathy. It is well tolerated but expensive.
- Probiotics (e.g., 1 capsule containing 112.5 billion viable lyophilized bacteria tid) might also be beneficial in altering gut flora to reduce ammonia production.

##### Treatment of cerebral edema:

- Cerebral edema is often present in patients with acute liver failure, and it accounts for nearly 50% of deaths. Monitoring intracranial pressure by epidural, intraparenchymal, or subdural transducers and treatment of cerebral edema with mannitol (100 to 200 ml of 20% solution [0.3 to 0.4 g/kg of body weight]) given by rapid IV infusion are helpful in selected patients (e.g., potential transplantation patients).
- Dexamethasone and hyperventilation (useful in head injury) are of little value in treating cerebral edema from liver failure.

#### CHRONIC Rx

- Avoidance of any precipitating factors (e.g., high-protein diet, medications).
- Consideration of liver transplantation in selected patients with progressive or recurrent encephalopathy (Box H1-4). Liver transplantation remains the only curative therapeutic option.

#### DISPOSITION

Prognosis varies with the underlying etiology of the liver failure and the grade of encephalopathy (generally good for grades 1 or 2; poor for grades 3 or 4). Without proper therapy, the survival rate at 1 yr is 42% and decreases to 23% at 3 yr.

#### REFERRAL

The early stages of hepatic encephalopathy can be managed in the outpatient setting, whereas stages 3 or 4 require hospital admission.

#### PEARLS & CONSIDERATIONS

##### COMMENTS

- Long-acting benzodiazepines should not be used to treat anxiety and sleep disorders in patients with cirrhosis, as they may precipitate encephalopathy.
- Patients not responding to supportive therapy should be evaluated for liver transplantation.
- Not all patients with cirrhosis develop hepatic encephalopathy. It has been shown that 40% of persons with cirrhosis and minimal hepatic encephalopathy do not develop overt hepatic encephalopathy in long-term follow-up. There are genetic factors associated with development of hepatic encephalopathy in patients with cirrhosis. Genetic analyses have shown that glutaminase TACC and CACC haplotypes are linked to the risk for overt hepatic encephalopathy.

#### EVIDENCE

Available at [www.expertconsult.com](http://www.expertconsult.com)

#### SUGGESTED READINGS

Available at [www.expertconsult.com](http://www.expertconsult.com)

#### RELATED CONTENT

Hepatic Encephalopathy (Patient Information)  
Cirrhosis (Related Key Topic)  
Encephalopathy (Related Key Topic)

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## EVIDENCE

### Abstract<sup>[1]</sup>

#### Background & Aims:

Patients with cirrhosis and minimal hepatic encephalopathy (MHE) have driving difficulties, but the effects of therapy on driving performance is unclear. We evaluated whether performance on a driving simulator improves in patients with MHE after treatment with rifaximin.

#### Methods:

Patients with MHE who were current drivers were randomly assigned to placebo or rifaximin groups and followed up for 8 weeks ( $n = 42$ ). Patients underwent driving simulation (driving and navigation tasks) at the start (baseline) and end of the study. We evaluated patients' cognitive abilities, quality of life (using the Sickness Impact Profile), serum levels of ammonia, levels of inflammatory cytokines, and model for end-stage-liver disease scores. The primary outcome was the percentage of patients who improved in driving performance, calculated as follows: total driving errors = speeding + illegal turns + collisions.

#### Results:

Over the 8-week study period, patients given rifaximin made significantly greater improvements than those given placebo in avoiding total driving errors (76% versus 31%;  $P = .013$ ), speeding (81% versus 33%;  $P = .005$ ), and illegal turns (62% versus 19%;  $P = .01$ ). Of patients given rifaximin, 91% improved their cognitive performance, compared with 61% of patients given placebo ( $P = .01$ ); they also made improvements in the psychosocial dimension of the Sickness Impact Profile compared with the placebo group ( $P = .04$ ). Adherence to the assigned drug averaged 92%. Neither group had changes in ammonia levels or model for end-stage-liver disease scores, but patients in the rifaximin group had increased levels of the anti-inflammatory cytokine interleukin-10.

#### Conclusions:

Patients with MHE significantly improve driving simulator performance after treatment with rifaximin, compared with placebo. **A**

### Abstract<sup>[2]</sup>

#### Background & Aims:

The risk of exacerbating sub-clinical hepatic encephalopathy (HE) by propofol has not been established. The aim of this study is to determine whether the use of propofol, for upper endoscopy in patients with cirrhosis, precipitates subclinical HE.

#### Methods:

Sixty-one patients with compensated HCV and HBV cirrhosis (CP score 5 to 6) were randomly selected and divided into two groups (intent-to-treat population) matched for age, gender, and BMI. The first group received a single propofol sedation ( $N = 31$ , age  $57 \pm 12$ , dose range 70 to 100 mg/procedure) and the second group ( $N = 30$ , age  $56 \pm 12$ , dose 3 to 6 mg/procedure) received a single midazolam sedation, all done by an anesthesiologist. All patients completed number connection test (NCT), cognitive function score, time to recovery, time to discharge sheets, and hemodynamic parameters before sedation, and at discharge from the

endoscopy unit, 1 h postprocedure. Thirty control subjects without cirrhosis were matched to the cirrhotic patients who received sedation with regard to age, gender, BMI, and education level.

#### Results:

A total of 58/61 cirrhotic patients (95%) had sub-clinical encephalopathy before the endoscopy (mean NCT  $84.7 \pm 77$  s, normal  $<30$  s). No patient developed overt HE after sedation. There were no differences between groups in the incidence of adverse effects, cognitive function, MELD score, CP score, oxygen saturation, or respiratory and heart rates before and after sedation. Propofol did not exacerbate minimal HE when compared with midazolam (NCT changed from  $87.5 \pm 62$  s before sedation to  $74.2 \pm 58$  s after sedation in the propofol group versus  $72.8 \pm 62$  s before to  $85.6 \pm 72$  s after sedation in the midazolam group;  $p < 0.01$ ). Time to recovery ( $4.1 \pm 1.9$  min versus  $11.5 \pm 5.0$  min,  $p < 0.001$ ), and time to discharge ( $38.0 \pm 9$  min versus  $110 \pm 42$  min,  $p < 0.001$ ) were significantly shorter with propofol than midazolam. Pre- and post-procedure NCT (from  $25 \pm 0$  s to  $24 \pm 20$  s), cognitive function score (from 25 to 26), time to recovery ( $3.5 \pm 1.0$  min), and time to discharge ( $35 \pm 10$  min) did not change in the healthy controls.

#### Conclusions:

Sedation with propofol has a shorter time recovery and a shorter time to discharge than midazolam and does not exacerbate sub-clinical hepatic encephalopathy in patients with compensated liver cirrhosis. **A**

## Evidence-Based References

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## BASIC INFORMATION

### DEFINITION

Hepatitis A is generally an acute self-limiting infection of the liver by an enterically transmitted picornavirus, hepatitis A virus (HAV). Infection may range from asymptomatic to fulminant hepatitis.

### SYNOMYS

Infectious hepatitis  
Short incubation hepatitis  
Type A hepatitis  
HAV (hepatitis A virus)

#### ICD-9CM CODES

070.1 Hepatitis A

#### ICD-10CM CODES

B15.9 Hepatitis A without hepatic coma

B15.0 Hepatitis A with hepatic coma

### EPIDEMIOLOGY & DEMOGRAPHICS

#### INCIDENCE

- Hepatitis A occurs worldwide, affecting 1.4 million people annually and accounting for 20% to 40% of cases of viral hepatitis in the United States.
- The seroprevalence increases with age, ranging from 10% in individuals aged <5 yr to 74% in those aged >50 yr.
- In the United States, average disease rate was ~15 cases/100,000 persons/yr before routine vaccination of all children in certain states. The incidence after 2005 is about 1 case/100,000.
- The incidence is relatively higher in some regions in the United States, including Arizona, Alaska, California, Idaho, Nevada, New Mexico, Oklahoma, Oregon, South Dakota, and Washington.
- At-risk groups include:
  - Residents and staff of group homes.
  - Children and employees of day care centers.
  - People who engage in oral-anal contact, regardless of sexual orientation.
  - IV drug abusers.
  - Travel to endemic areas.
  - Areas of overcrowding, poor sanitation, inadequate sewage treatment.

#### PREVALENCE

- Approximately three fourths of the U.S. population has serologic evidence of prior infection.
- Anti-HAV prevalence has an inverse relation to income and household size.

**PREDOMINANT SEX:** None, except higher infection rates seen in homosexual males who engage in oral-anal contact.

#### PREDOMINANT AGE/PEAK INCIDENCE

- In areas of high rates of hepatitis A, virtually all children are infected while younger than 10 yr, but disease is rare.
- In areas of moderate rates of hepatitis A, disease occurs in late childhood and young adults.
- In areas of low rates of hepatitis A, most cases occur in young adults.

**INCUBATION PERIOD:** Averages 30 days (15 to 50)

### PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Infection with HAV may have acute or subacute presentation, icteric or anicteric. Severity of illness seems to increase with age (90% of infection in children aged <5 yr may be subclinical).
- A preicteric, prodromal phase of approximately 1 to 14 days; 15% no apparent prodrome. Symptoms are usually abrupt in onset and may include anorexia, malaise, nausea, vomiting, fever, headache, and abdominal pain.
- Less common symptoms are chills, myalgias, arthralgias, upper respiratory symptoms, constipation, diarrhea, pruritus, urticaria.
- Jaundice occurs in >70% of patients.
- The icteric phase is preceded by dark urine.
- Bilirubinuria is typically followed a few days later by clay-colored stools and icterus.

### PHYSICAL EXAMINATION

- Jaundice: Peaks in severity 2 wk after onset.
- Hepatomegaly.
- Splenomegaly.
- Cervical lymphadenopathy.
- Evanescence rash.
- Petechiae.
- Cardiac arrhythmias.

### COMPLICATIONS

- Cholestasis.
- Fulminant hepatitis.
- Arthritis.
- Myocarditis.
- Optic neuritis.
- Transverse myelitis.
- Thrombocytopenic purpura.
- Aplastic anemia.
- Red cell aplasia.
- Henoch-Schönlein purpura.
- IgA dominant glomerulonephritis.

### ETIOLOGY

- Caused by HAV, a 27-nm, nonenveloped, icosahedral, positive-stranded RNA virus.
- Transmission is fecal-oral route, from person to person. Transmission occurs with close contact or with food- or water-borne outbreaks with inadequately purified water or cooked foods. Recent outbreaks have involved green onions and tomatoes.
- Parenteral transmission is considered rare.
- Vertical transmission has also been reported.

## DIAGNOSIS

### DIFFERENTIAL DIAGNOSIS

- Other hepatitis virus (B, C, D, E).
- Infectious mononucleosis.
- Cytomegalovirus infection.
- Herpes simplex virus infection.
- Leptospirosis.
- Brucellosis.
- Drug-induced liver disease.
- Ischemic hepatitis.
- Autoimmune hepatitis.

### WORKUP

- IgM antibody specific for HAV.
- Liver function tests; ALT and AST elevations are sensitive for liver damage but not specific for HAV.
- Elevated ESR.
- CBC; may find mild lymphocytosis.

### LABORATORY TESTS

- Diagnosis confirmed by IgM anti-HAV; it is detectable in almost all infected patients at presentation and remains positive for 3 to 6 mo.
- A fourfold rise in titer of total antibody (IgM and IgG) to HAV confirms acute infection.
- HAV detection in stool and body fluids by electron microscopy.
- HAV RNA detection in stool, body fluids, serum, and liver tissue.
- ALT and AST usually more than 8 times normal in acute infection.
- Bilirubin usually 5 to 15 times normal.
- Alkaline phosphatase minimally elevated but higher level in cholestasis.
- Albumin and prothrombin time are generally normal; if elevated, they may herald hepatic necrosis.
- Fig. H1-28** illustrates the typical course of hepatitis A.

### IMAGING STUDIES

- Rarely useful.
- Sonogram (fulminant hepatitis).

## TREATMENT

- Usually self-limited.
- Supportive care.
- Those with fulminant hepatitis may require hospitalization and treatment of associated complications.
- Activity as tolerated.
- Advise to avoid alcohol and hepatotoxic drugs.
- Patients with fulminant hepatitis should be assessed for liver transplantation.

### CHRONIC Rx

No chronic HAV and no chronic carrier state.

### DISPOSITION

- Follow-up as outpatient.
- Most patients recover within 2 months of infection, although 10% to 15% of patients will experience a relapse in the first 6 months.
- HAV is a self-limited infection and does not cause chronic hepatitis.

### REFERRAL

- To a hepatologist if severe, fulminant hepatitis develops
- To a transplant surgeon if liver transplant becomes a consideration for fulminant hepatitis and liver failure



## PEARLS & CONSIDERATIONS

- All cases of hepatitis A should be reported to the public health authorities because food-borne or water-borne outbreaks may occur, and public health efforts (mass vaccination or immunoglobulin therapy) may prevent secondary cases.
- Hepatitis A is a common illness in internationally traveled and developing countries. Pretravel vaccination is strongly recommended for travelers who are HAV susceptible.

## PREVENTION

- Improvement in hygiene and sanitation.
- Heating food.
- Avoidance of water and foods from endemic area.

## PASSIVE IMMUNIZATION

- Immunoglobulin provides protection against HAV through passive transfer of antibody.
- Preeexposure prophylaxis indicated for people traveling to endemic areas (Ig 0.02 or 0.06 ml/kg given IM) and have not received or cannot receive the hepatitis A vaccine before departure. The lower dose is effective for up to 3 mo, and the higher dose is effective for up to 5 mo.
- Postexposure prophylaxis (Ig 0.02 ml/kg given IM) is indicated for people with recent exposure (within 2 wk) to HAV and who have not been previously vaccinated. In high-risk patients, vaccine may be administered with immunoglobulin.

## ACTIVE IMMUNIZATION

- There are several inactivated and attenuated hepatitis vaccines; only the inactivated vaccines are currently available for use and

they have been found to be safe and highly immunogenic: HAVRIX or VAQTA. These can be used in adults and children older than 12 mo. They are given as a two-dose regimen 6 mo to 1 yr apart. A combined hepatitis A and hepatitis B vaccine called TWINRIX is also available.

- Protective antibody levels were reached in 94% to 100% of adults 1 mo after the first dose; similar results have been found for children and adolescents.
- Theoretic analyses of antibody levels estimate duration of immunity to be 10 to 20 yr.
- Vaccine should be considered for persons who are at risk: those traveling to or working in endemic areas, homosexual men, illegal drug users, persons with chronic liver disease, children in areas with high rates of hepatitis A infection.
- The Advisory Committee on Immunization Practices recommends routine hepatitis A vaccination for all children beginning at 12 to 23 mo of age.
- Clinical trials have shown equivalency between use of Ig and hepatitis A vaccine for postexposure prophylaxis in preventing symptomatic hepatitis A in healthy persons 2 to 40 yr of age. The Advisory Committee guidelines now provide for the use of Ig or the vaccine for this population. Those patients who are immunocompromised, have chronic liver disease, or are <1 yr of age should receive Ig.

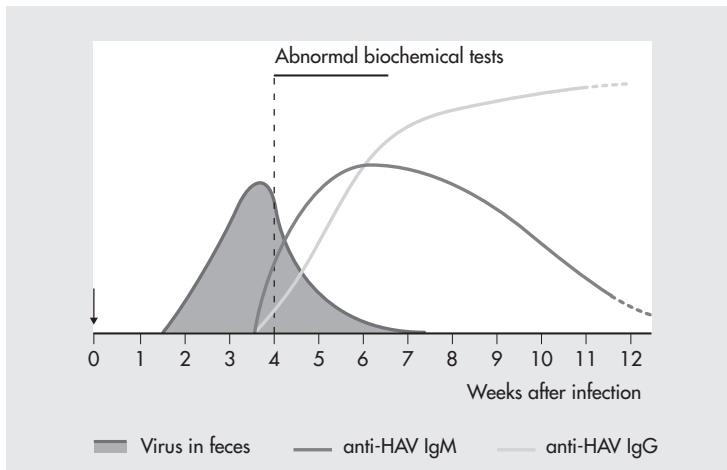
## SUGGESTED READINGS

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## RELATED CONTENT

Hepatitis A (Patient Information)

AUTHOR: GLENN G. FORT, M.D., M.P.H.



**FIGURE H1-28 Course of acute hepatitis A.** (From Cohen J, Powderly WG: *Infectious diseases*, ed 2, St Louis, 2004, Mosby.)

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## BASIC INFORMATION

### DEFINITION

Hepatitis B is an acute infection of the liver parenchymal cells caused by the hepatitis B virus (HBV).

### SYNOMYS

Serum hepatitis

Long incubation (30 to 180 days) hepatitis

### ICD-9CM CODES

070.3 Hepatitis B

### ICD-10CM CODES

B16 Acute hepatitis

B16.9 Acute hepatitis B without delta agent and without hepatic coma

B16.1 Acute hepatitis B with delta agent (coinfection) without hepatic coma

B18.0 Chronic hepatitis B with delta agent

B18.1 Chronic hepatitis B without delta agent

B19.10 Unspecified viral hepatitis B without hepatic coma

### EPIDEMIOLOGY & DEMOGRAPHICS

#### INCIDENCE (IN U.S.):

- ~200,000 to 300,000 infections annually in the United States.
- Much higher incidence in Europe (~1 million new cases annually) and in areas of high endemicity.
- In the United States, transmission is mainly horizontal (percutaneous and mucous membrane exposure to infectious blood and other body fluids [e.g., sexual transmission, either homosexual or heterosexual]; also from needle sharing among drug abusers; occupational exposure to contaminated blood and blood products; persons receiving transfusions of blood and blood products; and hemodialysis patients).

**NOTE:** Improved screening of blood and blood products has greatly reduced, although not eliminated, the risk of posttransfusion HBV infection.

- In areas of high endemicity, transmission is largely vertical (perinatal): HBV exists in the blood and body fluids. Perinatal transmission from HBsAg-positive mothers is as high as 90% unless immunoprophylaxis is given.

#### PREVALENCE (IN U.S.)

- The WHO estimates that 400 million people worldwide (6% of the population) are chronic HBV carriers. North America, Western Europe, and Australia are areas of low prevalence, <2%. In the United States an estimated 800,000 to 1.4 million people have chronic HBV infection.
- Africa, Asia, and the Western Pacific region are areas of high prevalence, ≥8%.
- Southern and Eastern Europe have intermediate rates, 2% to 7%.
- Chronically infected persons, those with positive HBsAg for >6 mo, represent the major source of infection.

- As many as 95% of infants and children aged <5, who typically have subclinical acute infection, will become chronic HBV carriers.
- Adults are more likely to have clinically evident acute infection, but only 1% to 5% will develop chronic infection.
- ~0.1% of patients with acute infection will develop fulminant acute hepatitis resulting in death.

### PREDOMINANT SEX

- Predominant in males because of increased IV drug abuse, homosexuality.
- Females more commonly terminate in chronic carrier state.

### PREDOMINANT AGE: 20 to 45 yr.

### PEAK INCIDENCE: 30 to 45 yr of age, at rates of 5% to 20%.

### GENETICS: Neonatal infection:

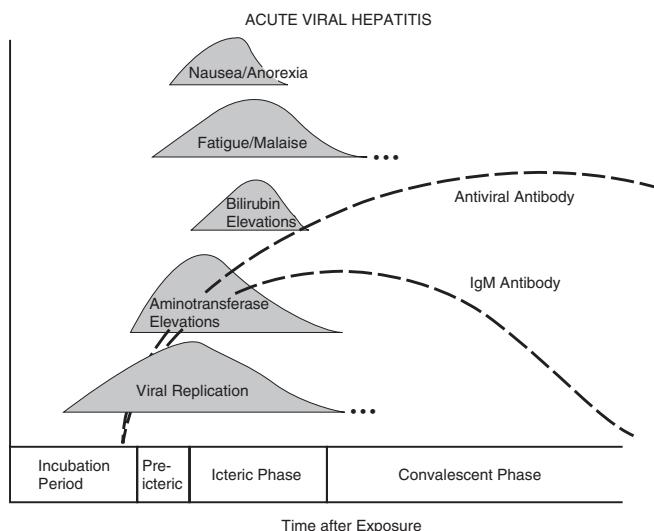
- Rare in the United States.
- High (up to 90%) in areas of high endemicity (only 5% to 10% of perinatal infections occur in utero).

### PHYSICAL FINDINGS & CLINICAL PRESENTATION (Fig. H1-29)

- Often nonspecific symptoms.
- Profound malaise.
- Many asymptomatic cases.
- Prodrome:
  - 15% to 20% serum sickness (urticaria, rash, arthralgia) during early HBsAg.
  - HBsAg-Ab complex disease (polyarteritis nodosa–arthritis, arteritis, glomerulonephritis).
  - Hepatomegaly (87%) with right upper quadrant (RUQ) tenderness.
    1. Hepatic punch tenderness.
    2. Splenomegaly: rare (10% to 15%).
  - Jaundice, dark urine, with occasional pruritus.
  - Variable fever (when present, generally precedes jaundice and rapidly declines following onset of icteric phase).
  - Spider angioma: rare; resolves during recovery.
  - Rare polyarteritis nodosa, cryoglobulinemia.

### ETIOLOGY

- Caused by HBV (42-nm hepadnavirus with an outer surface coat [HBsAg], inner nucleocapsid core [HBcAg; HBeAg]; DNA polymerase; and partially double-stranded DNA genome). There are eight genotypes (A to H) based on nucleotide sequence. The prevalence of each genotype varies widely.
- Transmission by parenteral route (needle use, tattooing, ear piercing, acupuncture, transfusion of blood and blood products, hemodialysis, sexual contact), perinatal transmission.
- Infection may result from contact of infectious material with mucous membranes and open skin breaks (e.g., HBV is stable and can be transmitted from toothbrushes, utensils, razors, baby toys, assorted medical equipment [respirators, endoscopes]).
- Oral intake of infectious material may result in infection through breaks in the oral mucosa.
- Food or water are virtually never found to be sources of HBV infection.
- Infection occurs primarily in liver, where necrosis probably results from cytotoxic T-cell response, direct cytopathic effect of HBcAg (core antigen), high-level HBsAg (surface antigen) expression, or coinfection with delta (D) hepatitis virus (RNA delta core within HBsAg envelope).
- Recovery (>90%):
  - Fulminant hepatitis occurring in <1% (especially if coinfected with hepatitis D); 80% fatal.
  - Unusual (5%) prolonged acute disease for 4 to 12 mo, with recovery.
  - Overall fatality increases with age and viral inoculation (e.g., transfusions).
- Chronic infection (1% to 2%):
  - Persistent carrier state without hepatitis (HBsAg positive).
  - Chronic persistent hepatitis (CPH) (clinically well), or chronic active hepatitis (CAH) (HBsAg positive and HBeAg positive).



**FIGURE H1-29 The typical course of acute viral hepatitis.** (From Goldman L, Ausiello D [eds]: *Cecil textbook of medicine*, ed 22, Philadelphia, 2004, Saunders.)

3. Cirrhosis.
4. Hepatocellular carcinoma (especially after neonatal infection).
5. Chronic infection: more common following low-dose exposure and mild acute hepatitis, with earlier age of infection, in males, and in immunosuppressed patients.
6. One third to one quarter of chronically infected will develop progressive liver disease (cirrhosis, hepatocellular carcinoma).

## Dx DIAGNOSIS

### DIFFERENTIAL DIAGNOSIS

- Acute disease confused with other viral hepatitis infections (A, C, D, E).
- Any viral illness producing systemic disease and hepatitis (e.g., yellow fever, EBV, CMV, HIV, rubella, rubeola, coxsackie B, adenovirus, herpes simplex or zoster).
- Nonviral causes of hepatitis (e.g., leptospirosis, toxoplasmosis, alcoholic hepatitis, drug-induced [e.g., acetaminophen, INH], toxic hepatitis [carbon tetrachloride, benzene]).

### WORKUP

- Acute serum specimen for hepatitis B serology (HBsAg, HBsAb, HBcAb, HBeAg, HBeAb), HBDNA by PCR.
- LFTs.
- CBC.
- Liver biopsy: rarely indicated for diagnosis of fulminant viral hepatitis, chronic hepatitis, cirrhosis, carcinoma.

### LABORATORY TESTS

- Diagnosis of acute HBV infection is best confirmed by IgM HBcAb in acute or early convalescent serum or by HBDNA by PCR.
  1. Generally, IgM present during onset of jaundice.
  2. Coexisting HBsAg.
- HBsAg and IgG-HBcAb during acute jaundice are strongly suggestive of remote HBV infec-

tion and another cause for current illness (Fig. H1-30).

- HBsAb alone is suggestive of immunization response.
- With recovery, HBeAg is rapidly replaced by HBeAb in 2 to 3 mo, and HBsAg is replaced by HBsAb in 5 to 6 mo.
- In chronic HBV hepatitis, HBsAg and HBeAg are persistent without corresponding Ab.
- In chronic carrier state, HBsAg is persistent, but HBeAg is replaced by HBeAb.
- HBcAb develops in all outcomes.
- HBeAg correlation with highest infectivity; appearance of HBeAb heralds recovery.
- LFTs:

1. ALT and AST: usually more than eight times normal (often 1000 U/L) at onset of jaundice (minimal acute ALT/AST rises often followed by chronic hepatitis or hepatocellular carcinoma).
2. Bilirubin: variably elevated in icteric viral hepatitis.
3. Alkaline phosphatase: minimally elevated (one to three times normal) acutely.
- Albumin and prothrombin time:
  1. Generally normal.
  2. If abnormal, possible harbinger of impending hepatic necrosis (fulminant hepatitis).
- WBC and ESR: generally normal.

### IMAGING STUDIES

- Rarely useful.
- Sonogram to document rapid reduction in liver size during fulminant hepatitis or mass in hepatocellular carcinoma.

## Rx TREATMENT

### NONPHARMACOLOGIC THERAPY

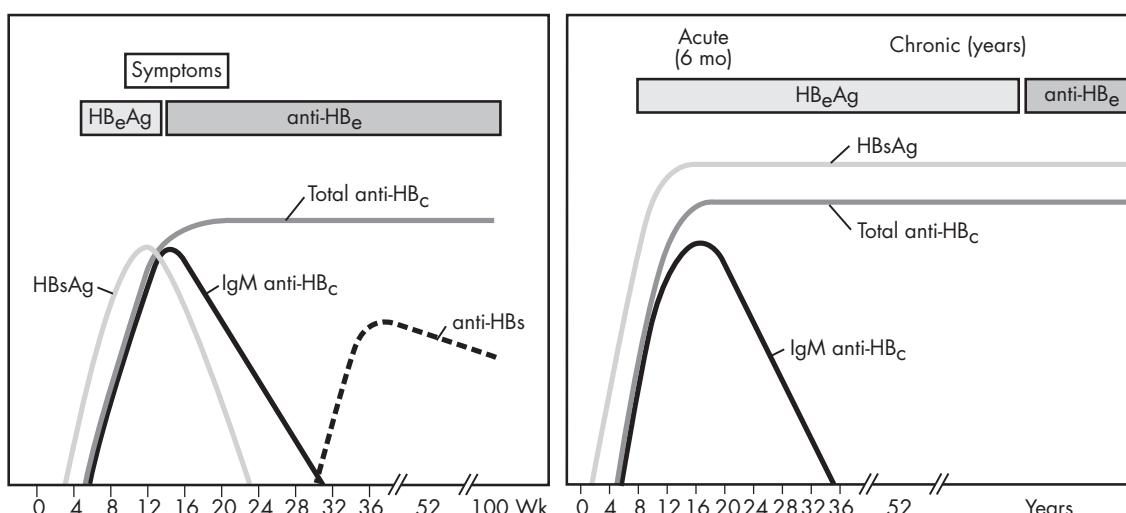
- Symptomatic treatment as necessary.
- Activity as tolerated.
- High-calorie diet preferred; often best tolerated in morning.

### ACUTE GENERAL Rx

- In most cases of acute HBV infection no treatment necessary; >90% of adults will spontaneously clear infection.
- Hospitalization advisable for any patient in danger from dehydration caused by poor oral intake, whose PT is prolonged, who has rising bilirubin level >15 to 20 µg/dL, or who has any clinical evidence of hepatic failure.
- IV therapy needed (rarely) for hydration during severe vomiting.
- Avoid hepatically metabolized drugs.
- No therapeutic measures are beneficial.
- Steroids not shown helpful.

### CHRONIC Rx

- The American Association for the Study of Liver Diseases issued guidelines in 2009 for the evaluation and treatment of hepatitis B.
- The aim of therapy in chronic HBV infection is to eradicate the virus. Treatment is recommended in patients with HbeAg-positive or HbeAg-negative chronic hepatitis and in patients with compensated cirrhosis and HBV DNA > 2000 IU/ml and those with decompensated cirrhosis and detectable HBV DNA by PCR regardless of the serum ALT level.
- The two modalities of therapy available to achieve this goal have been immune modulators (interferon alfa) and antiviral agents in the form of nucleoside analogues (e.g., lamivudine).
- PEGylated interferon alpha (IFN- $\alpha$ ) given as a once-a-week SQ injection for 48 wk is a mainstay of therapy and has largely replaced interferon alpha without pegylation, which required daily or thrice weekly injections. Its mechanism of action is to stimulate the immune system to attack HBV-infected hepatocytes, thus inhibiting viral protein synthesis. Dose: 180 µg SQ weekly.
- A 12-mo course of treatment results in a 30% to 40% response with significant reduction of serum HBV DNA, normalization of ALT,



**FIGURE H1-30 Typical course of hepatitis B.** *Left*, Typical course of acute hepatitis B. *Right*, Chronic hepatitis B. HBc, Hepatitis B core; HBe, hepatitis B early; HBsAg, hepatitis B surface antigen; IgM, immunoglobulin M. (From Mandell GL et al: *Principles and practice of infectious diseases*, ed 7, Philadelphia, 2010, Saunders.)

- and loss of HBeAg. Seroconversion from HBeAg to HBeAb occurs in 15% to 20%.
- Factors that increase the likelihood of response to IFN- $\alpha$  therapy include:
    - Adult onset of infection.
    - High baseline ALT.
    - Low baseline HBV DNA.
    - Absence of cirrhosis.
    - Female.
    - HBeAg positive.
  - Infrequent relapse after successful completion of therapy.
  - 80% of patients who lose HBeAg during therapy lose HBsAg in the decade after therapy.
  - >50% of patients who do not seroconvert after initial therapy develop a delayed HBeAg seroconversion months to years after therapy.
  - Overall incidence of cirrhosis and hepatocellular carcinoma is decreased in those treated with IFN- $\alpha$ .
  - IFN- $\alpha$  is successful only in patients with an active immune response; therefore it is not effective in patients with HIV infection and organ transplant patients.
  - Asians respond poorly to IFN- $\alpha$ . Patients with genotype A respond well to IFN- $\alpha$ .
  - Treatment with IFN- $\alpha$  in general is not well tolerated: side effects include flulike symptoms, injection-site reactions, rash, weight loss, anxiety, depression, alopecia, thrombocytopenia, granulocytopenia, and thyroid dysfunction.
  - Nucleoside analogues block viral replication by inhibiting HBV polymerase and require lifelong treatment.
  - Lamivudine is the first nucleoside analogue approved for treatment of chronic HBV infection; it has been shown to rapidly reduce HBV replication and suppress HBV DNA to undetectable levels after a few wk of treatment, and treatment for 1 yr is as effective as IFN- $\alpha$  with respect to loss of HBeAg seroconversion to HBeAb and loss of HBV DNA. The high rate of emergence of resistant HBV strains on therapy has limited the use of lamivudine as a first-line agent (YMDD variants [tyrosine-methionine-aspartate-aspartate]). Dose: 100 mg orally daily with normal kidney function.
  - Adefovir dipivoxil: 10 mg orally daily with normal kidney function is a nucleotide reverse transcriptase inhibitor that also has antiviral activity against HBV. It is a prodrug that is

converted to the active drug adefovir. It is highly active against HBV and may be useful as a first-line agent or as salvage therapy for patients who are refractory or intolerant to lamivudine. (Nephrotoxicity is a potential side effect, but emergence of resistant strains is less so than with lamivudine.)

- Entecavir is a potent nucleoside agent approved for the treatment of hepatitis B, and it appears to be more effective and to present fewer concerns than lamivudine or adefovir regarding the emergence of resistant strains. Dose: 0.5 mg PO daily for nucleoside-naïve patients and 1 mg PO daily for lamivudine-resistant patients.
- Telbivudine, a thymidine nucleosidase analogue, is more potent than lamivudine or adefovir after 24 wk of treatment but selects for the same resistant strains as lamivudine. Dose: 600 mg PO daily.
- Tenofovir: more potent than adefovir and suppresses lamivudine, telbivudine, or entecavir resistant strains. In the United States it has become a first-line agent. Dose: 300 mg daily with normal kidney function.
- Combination therapy with two or three nucleoside analogues or combination therapy with IFN- $\alpha$  is currently under investigation.
- Liver transplantation (should be considered for fulminant hepatitis).

## DISPOSITION

- Follow-up as outpatient.
- Acute disease: usually <6 wk.
- Rare fatalities (fulminant hepatitis).
- Possible chronic carrier state, cirrhosis, hepatocellular carcinoma.

## REFERRAL

To infectious disease specialist and gastroenterologist for consultation regarding fulminant hepatitis or prolonged cholestasis, for cases of uncertain etiology, or for treatment of CAH.

## PEARLS & CONSIDERATIONS

### COMMENTS

- Virus and HBsAg in high titers in blood for 1 to 7 wk before jaundice and for a variable time thereafter.
- Transmission is possible during entire period of HBsAg (and especially during HBeAg) in serum.

- Universal precautions should be followed for all contacts with blood or secretions/excretions contaminated with blood.
- Preventing before exposure:
  - Lifestyle changes
  - Meticulous testing of blood supply (although some chronically infected, infectious donors are HBsAg negative).
  - Sterilization via steam or hypochlorite.
  - Hepatitis B vaccine for high-risk groups given IM in deltoid to induce HBsAb (response should be confirmed) is protective (>90% effective).
  - Recommendation for universal childhood immunization with doses at birth, 1 mo, and 6 mo.
- Prevention after exposure:
  - HBV hyperimmune globulin (HBIG) (0.06 ml/kg IM) given immediately after needlestick, within 14 days of sexual exposure, or at birth, followed by HBV vaccination. A second dose of HBIG is given in 28 days for those refusing vaccine or vaccine nonresponders.
  - Standard immune globulin: nearly as effective as HBIG
- Preventive therapy with lamivudine or entecavir or tenofovir for patients who test positive for HBsAg and are undergoing chemotherapy may reduce the risk for HBV reactivation and HBV-associated morbidity and mortality.
- Hepatitis B prophylaxis is described in Section V.
- Table H1-17** summarizes interpretation of serologic markers and serum DNA in hepatitis B.

## EBM EVIDENCE

Available at [www.expertconsult.com](http://www.expertconsult.com)

## SUGGESTED READINGS

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## RELATED CONTENT

Fig. 3-94 A flow diagram showing the use of specific serologic tests for the diagnosis of acute viral hepatitis in relation to the clinical and epidemiologic setting (Algorithm) Hepatitis B (Patient Information)

AUTHOR: GLENN G. FORT, M.D., M.P.H.

**TABLE H1-17** Interpretation of Serologic Markers and Serum DNA in Hepatitis B

	HBsAg	HbeAg	Anti-HBc IgM	Anti-HBc IgG	Anti-HBs	Anti-HBe	HBV DNA*
Acute hepatitis	+	+/-	+				+
Acute hepatitis, window period			+				
Recovery from acute hepatitis			+	+	+	+/-	
Chronic hepatitis	+	+					+
Chronic hepatitis (precore mutant)	+					+	+
Inactive carrier	+					+/-	
Vaccinated							+

HBsAg, Hepatitis B surface antigen; HBeAg, hepatitis Be antigen; anti-HBc IgM, hepatitis B core antibody (IgM type); anti-HBc IgG, hepatitis B core antibody (IgG type); anti-HBs, hepatitis B surface antibody; anti-HBe, hepatitis Be antibody; HBV DNA, hepatitis B viral DNA.

\*HBV DNA >10<sup>5</sup> copies/ml.

From Andreoli TE et al: *Andreoli and Carpenter's Cecil essentials of medicine*, ed 8, Philadelphia, 2010, Saunders.



## EVIDENCE

### Abstract<sup>[1]</sup>

#### Background:

Despite limited prospective data, it is commonly believed that human immunodeficiency virus (HIV) and hepatitis infections are widespread in the penetrating trauma population, placing healthcare workers at risk for occupational exposure. Our primary study objective was to measure the prevalence of HIV (anti-HIV), hepatitis B (HB surface antigen [HBsAg]), and hepatitis C virus (anti-HCV) in our penetrating trauma population.

#### Methods:

We prospectively analyzed penetrating trauma patients admitted to Temple University Hospital between August 2008 and February 2010. Patients ( $n = 341$ ) were tested with an oral swab for anti-HIV and serum evaluated for HBsAg and anti-HCV. Positives were confirmed with Western blot, neutralization immunoassay, and reverse transcription polymerase chain reaction, respectively. Demographics, risk factors, and clinical characteristics were analyzed.

#### Results:

Of 341 patients, 4 patients (1.2%) tested positive for anti-HIV and 2 had a positive HBsAg (0.6%). Hepatitis C was the most prevalent measured infection as anti-HCV was detected in 26 (7.6%) patients. Overall, 32 (9.4%) patients tested positive for anti-HIV, HBsAg, or anti-HCV. Twenty-eight (75%) of these patients who tested positive were undiagnosed before study enrollment. When potential risk factors were analyzed, age (odds ratio, 1.07,  $p = 0.031$ ) and intravenous drug use (odds ratio 14.4,  $p < 0.001$ ) independently increased the likelihood of anti-HIV, HBsAg, or anti-HCV-positive markers.

#### Conclusions:

Of our penetrating trauma study population, >9% tested positive for anti-HIV, HBsAg, or anti-HCV although patients were infrequently aware of their seropositive status. As penetrating trauma victims frequently require expedient, invasive procedures, universal precautions are essential. The prevalence of undiagnosed HIV and hepatitis in penetrating trauma victims provides an important opportunity for education, screening, and earlier treatment of this high-risk population.<sup>①</sup>

### Abstract<sup>[2]</sup>

#### Background:

Chronic infection with hepatitis B virus and hepatitis delta virus (HDV) results in the most severe form of viral hepatitis. There is no currently approved treatment. We investigated the safety and efficacy of 48 weeks of treatment with peginterferon alfa-2a plus adefovir dipivoxil, peginterferon alfa-2a alone, and adefovir dipivoxil alone.

#### Methods:

We conducted a randomized trial in which 31 patients with HDV infection received treatment with 180 µg of peginterferon alfa-2a weekly plus 10 mg of adefovir daily, 29 received 180 µg of peginterferon alfa-2a weekly plus placebo, and 30 received 10 mg of adefovir alone weekly for 48 weeks. Follow-up was conducted for an additional 24 weeks. Efficacy end points included clearance of HDV RNA, normalization of alanine aminotransferase levels, and a decline in levels of hepatitis B surface antigen (HBsAg).

#### Results:

The primary end point—normalization of alanine aminotransferase levels and clearance of HDV RNA at week 48—was achieved in two patients in the group receiving peginterferon alfa-2a plus adefovir and two patients in the group receiving peginterferon alfa-2a plus placebo but in none of the patients in the group receiving adefovir alone. At week 48, the test for HDV RNA was negative in 23% of patients in the first group, 24% of patients in the second, and none of those in the third ( $P = 0.006$  for the comparison of the first and third groups;  $P = 0.004$  for the comparison of the second and third). The efficacy of peginterferon alfa-2a was sustained for 24 weeks after treatment, with 28% of the patients receiving peginterferon alfa-2a plus adefovir or peginterferon alfa-2a alone having negative results on HDV-RNA tests; none of the patients receiving adefovir alone had negative results. A decline in HBsAg levels of more than 1 log<sub>10</sub> IU per milliliter from baseline to week 48 was observed in 10 patients in the first group, 2 in the second, and none in the third

( $P < 0.001$  for the comparison of the first and third groups and  $P = 0.01$  for the comparison of the first and second).

#### Conclusions:

Treatment with peginterferon alfa-2a for 48 weeks, with or without adefovir, resulted in sustained HDV RNA clearance in about one quarter of patients with HDV infection. (Funded by Hep-Net [the German Network of Excellence on Viral Hepatitis] and others; Current Controlled Trials number, ISRCTN83587695.)<sup>①</sup>

### Abstract<sup>[3]</sup>

#### Background & Aims:

Tenofovir disoproxil fumarate (TDF), a nucleotide analogue and potent inhibitor of hepatitis B virus (HBV) polymerase, showed superior efficacy to adefovir dipivoxil in treatment of chronic hepatitis B through 48 weeks. We evaluated long-term efficacy and safety of TDF monotherapy in patients with chronic hepatitis B who were positive or negative for hepatitis B e antigen (HBeAg+ or HBeAg-).

#### Methods:

After 48 weeks of double-blind comparison of TDF to adefovir dipivoxil, patients who underwent liver biopsy were eligible to continue the study on open-label TDF for 7 additional years; data presented were collected up to 3 years (week 144) from 85% of participants. Primary efficacy end points at week 144 included levels of HBV DNA and alanine aminotransferase, development of resistance mutations, and presence of HBeAg or hepatitis B surface antigen (HBsAg).

#### Results:

At week 144, 87% of HBeAg- and 72% of HBeAg+ patients treated with TDF had levels of HBV DNA <400 copies/mL. Among patients who had previously received adefovir dipivoxil and then received TDF, 88% of the HBeAg- and 71% of the HBeAg+ patients had levels of HBV DNA <400 copies/mL; overall, 81% and 74%, respectively, maintained normalized levels of alanine aminotransferase and 34% had lost HBeAg. Amino acid substitutions in HBV DNA polymerase that are associated with resistance to tenofovir were not detected in any patient. Cumulatively, 8% of HBeAg+ patients lost HBsAg. TDF maintained a favorable safety profile for up to 3 years.

#### Conclusions:

TDF was safe and effective in the long-term management of HBeAg+ and HBeAg- patients with chronic hepatitis B.<sup>①</sup>

## Evidence-Based References

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## BASIC INFORMATION

### DEFINITION

Hepatitis C is an acute liver parenchymal infection caused by hepatitis C virus (HCV).

### SYNOMYS

Transfusion-related non-A, non-B hepatitis (incubation period averages 6 wk, intermediate between hepatitis A and B)

#### ICD-9CM CODES

070.51 Other viral hepatitis

#### ICD-10CM CODES

B17.1 Acute hepatitis C

B18.2 Chronic viral hepatitis C

B17.10 Acute hepatitis C without hepatic coma

### EPIDEMIOLOGY & DEMOGRAPHICS

Hepatitis C infection is the most common chronic blood-borne infection in the United States. About 3% of baby boomers test positive for the virus. The CDC now recommends testing for hepatitis C for anyone born from 1945 to 1965. **INCIDENCE (IN U.S.):** HCV infects more than 185 million individuals worldwide. Approximately 20% of patients chronically infected with HCV progress to cirrhosis.

- 150,000 new cases/yr (37,500 symptomatic; 93,000 later chronic liver disease; 30,700 cirrhosis). The incidence of acute HCV has declined substantially over the past 30 yr (from 7.4/100,000 to 0.7/100,000).
- ~9000 of these ultimately die of HCV infection; most common (40%) cause of nonalcoholic liver disease in the United States

### PREVALENCE (IN U.S.)

- Overall prevalence of anti-HCV antibody is 1% to 1.2% (an estimated 2.7 million persons nationwide).
- Highest prevalence in hemophiliacs transfused before 1987 and users of injection drugs, 72% to 90%. Over past 30 yr, blood transfusion as a risk factor declined from 15% of cases to 1.9%.
- Among low-risk groups, prevalence 0.6%.

**PREDOMINANT SEX:** Slight male predominance. **PREDOMINANT AGE:** Highest prevalence in 30- to 49-yr age group (65%).

### PEAK INCIDENCE:

- 20 to 39 yr of age.
- African Americans and whites have similar incidence of acute disease; Hispanics have higher rates.
- Prevalence is substantially higher among non-Hispanic blacks than among non-Hispanic whites.

**GENETICS:** Neonatal infection is rare; increased risk with maternal HIV-1 coinfection.

### PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms usually develop 7 to 8 wk after infection (range of 2 to 26 wk), but 70% to 80% of cases are subclinical.
- 10% to 20% report acute illness with jaundice and nonspecific symptoms (abdominal pain, anorexia, malaise).

- Fulminant hepatitis may rarely occur during this period.

- After acute infection, 15% to 25% have complete resolution (absence of HCV RNA in serum, normal ALT).
- Progression to chronic infection is common, 50% to 84%. 74% to 86% have persistent viremia; spontaneous clearance of viremia in chronic infection is rare. 60% to 70% of patients will have persistent or fluctuating ALT levels; 30% to 40% with chronic infection have normal ALT levels.

- 15% to 20% of those with chronic HCV will develop cirrhosis over a period of 20 to 30 yr; in most others, chronic infection leads to hepatitis and varying degrees of fibrosis.
- 0.4% to 2.5% of patients with chronic infection develop hepatocellular carcinoma (HCC).
- 25% of patients with chronic infection continue to have an asymptomatic course with normal LFTs and benign histology.
- In chronic HCV infection, extrahepatic sequelae include a variety of immunologic and lymphoproliferative disorders (e.g., cryoglobulinemia, membranoproliferative glomerulonephritis, and possibly Sjögren's syndrome, autoimmune thyroiditis, polyarteritis nodosa, aplastic anemia, lichen planus, porphyria cutanea tarda, B-cell lymphoma, others).

### ETIOLOGY

- Caused by HCV (single-stranded RNA flavivirus).
- Most HCV transmission is parenteral.
- In the United States, advances in screening of blood and blood products have made transfusion-related HCV infection rare (the risk is estimated to be 0.001% per unit transfused).
- Injecting-drug use accounts for most HCV transmission in the United States (60% of newly acquired cases, 20% to 50% of chronically infected persons).
- Occupational needlestick exposure from an HCV-positive source has a seroconversion rate of 1.8% (range 0% to 7%).
- Nosocomial transmission rates (from surgery and procedures such as colonoscopy and hemodialysis) are extremely low.
- Sexual transmission and maternal-fetal transmission are infrequent (estimated at 5%).
- No identifiable risk in 40% to 50% of community-acquired hepatitis C, but snorting of cocaine by shared use of straw or rolled-up paper has been identified as a risk factor because it causes microscopic bleeding of nasal mucosa.
- HCV infection may stimulate production of cytotoxic T lymphocytes and cytokines (INF- $\gamma$ ), which probably mediate hepatic necrosis.

## Dx DIAGNOSIS

### DIFFERENTIAL DIAGNOSIS

- Other hepatitis viruses (A, B, D, E).
- Other viral illnesses producing systemic disease (e.g., yellow fever, EBV, CMV, HIV, rubella, rubella, coxsackie B, adenovirus, HSV, HZV).
- Nonviral hepatitis (e.g., leptospirosis, toxoplasmosis, alcoholic hepatitis, drug-induced hepatitis [acetaminophen, INH], toxic hepatitis).
- LFTs: ALT and AST may be elevated to more than eight times normal in acute infection; in chronic infection ALT may be normal or fluctuate.
- Bilirubin may be five to 10 times normal.
- Albumin and prothrombin time generally normal; if abnormal, may be harbinger of impending hepatic necrosis.

### WORKUP

- Acute hepatitis C antibody, viral genotyping, viral titers.
- LFTs; CBC.

NOTE: ALT is an easy and inexpensive test to monitor infection and efficacy of therapy. However, ALT levels may fluctuate or even be normal in active or chronic infection and even with cirrhosis, and ALT may remain elevated even after clearance of viremia.

- Liver biopsy with histologic staging is the gold standard for assessing the degree of disease activity and the likelihood of disease progression, and also to help rule out other causes of liver disease.

### LABORATORY TESTS

- Diagnosis is often by exclusion, because it takes 6 wk to 12 mo to develop anti-HCV antibody (70% positive by 6 wk, 90% positive by 6 mo).
- Diagnostic tests include serologic assays for antibodies and molecular tests for viral particles.

1. Enzyme immunoassay is the test for anti-HCV antibody:  
The current version can detect antibody within 4 to 10 wk after infection.

False-negative rate in low-risk populations is 0.5% to 1%.  
False negatives also occur in immune-compromised persons, HIV-1, renal failure, HCV-associated essential mixed cryoglobulinemia.

False positives in autoimmune hepatitis, paraproteinemia, and persons with no risk factors.

- The recombinant immunoblot assay that was previously recommended as a follow-up to positive antibody test is no longer available. The CDC now recommends that anyone who tests positive for HCV antibodies receive a follow-up HCV RNA test.

- Qualitative and quantitative HCV RNA tests using PCR: Lower limit of detection is <43 IU/ml.

- Used to confirm viremia and to assess response to treatment.

- Qualitative polymerase chain reaction (PCR) useful in patients with negative enzyme immunoassay in whom infection is suspected.

- Quantitative tests use either branched-chain DNA or reverse transcription PCR; the latter is more sensitive.

- Viral genotyping can distinguish among genotypes 1, 2, 3, and 4, which is helpful in choosing therapy; most of these tests use PCR (genotypes 1, 2, 3, and 4 predominate in the United States and Europe [genotype 1 is especially common in North America (60% to 75% of Hep C infections in the United States)]).

- LFTs: ALT and AST may be elevated to more than eight times normal in acute infection; in chronic infection ALT may be normal or fluctuate.
- Bilirubin may be five to 10 times normal.
- Albumin and prothrombin time generally normal; if abnormal, may be harbinger of impending hepatic necrosis.

- WBC and erythrocyte sedimentation rate (ESR) are generally normal.
- HIV testing.

### IMAGING STUDIES

Sonogram: rapid liver size reduction during fulminant hepatitis or mass in HCC.

## RX TREATMENT

### NONPHARMACOLOGIC THERAPY

Activity and diet as tolerated, avoid saw palmetto and green tea leaf herbs.

### ACUTE GENERAL Rx

- Supportive care.
- Avoid hepatically metabolized drugs.

### CHRONIC Rx

Response to therapy is influenced by HCV genotype. Patients with HCV genotype 1 can be treated with sofosbuvir + pegylated interferon + ribavirin because of the shorter duration of therapy and higher rates of sustained virologic response (SVR) (89% to 90%). Simeprevir + pegylated interferon + ribavirin is an alternative for patients with HCV genotype 1 (SVR 79% to 86%). Patients with genotypes 2 and 3 can be treated with sofosbuvir + ribavirin alone (SVR for genotype 2, 12 weeks' duration: 82% to 93%; SVR for genotype 3, 24 weeks' duration 80% to 95%).

- Currently, new all oral regimens of DAAs without interferon or ribavirin are available that have cure rates of more than 95%. These include ledipasvir + sofosbuvir for 12 weeks, daclatasvir + asunaprevir for 12 or 24 weeks and ABT-450/r-ombitasvir and dasabuvir with or without weight-based ribavirin for 12 weeks.

- Liver transplantation:
  1. Hepatitis C is the main indication for liver transplantation in the United States.
  2. It is the only option for patients with deteriorating HCV-related cirrhosis and for some patients with HCC.
  3. Recurrent infection occurs in almost all patients with progressive fibrosis and cirrhosis; as many as 20% progress to cirrhosis within 5 yrs posttransplant.

### DISPOSITION

- SVR after treatment among HCV-infected persons at any stage of fibrosis is associated with reduced HCC.
- Periodic abdominal ultrasonography for HCC screening.
- Recent guidelines recommend against measurement of alpha-fetoprotein (AFP) to screen for HCC in patients with chronic hepatitis C due to lack of sensitivity, specificity, and predictive values.

### REFERRAL

- To a hepatologist or infectious disease specialist for treatment for hepatitis C.
- To a transplant surgeon for consideration of liver transplant if indicated.

## PEARLS & CONSIDERATIONS

- More rapid progression of disease in persons who drink alcohol regularly, persons of advanced age at time of infection, and those coinfecte with other viruses (HIV, hepatitis B). All persons with identified HCV infection should receive a brief alcohol screening and intervention as clinically indicated.

- Major depression is a common (20%-40%) side effect of treatment with interferons. Use of the SSRI escitalopram has been found safe and effective for prevention of interferon-associated depression in these patients.

- Regression of cirrhosis has been demonstrated after antiviral therapy in some patients with chronic hepatitis C. Regression is associated with decreased disease-related morbidity and improved survival.

- The presence of interleukin (IL)-28B and HLA class II is independently associated with spontaneous resolution of HCV infection, and single nucleotide polymorphism IL-28B and DQB1\*03:01 may explain approximately 15% of spontaneous resolution of HCV infection.

### SUGGESTED READINGS

Available at [www.expertconsult.com](http://www.expertconsult.com)

### RELATED CONTENT

Hepatitis C (Patient Information)

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## BASIC INFORMATION

### DEFINITION

Hepatocellular carcinoma (HCC) is a malignant tumor of the hepatocytes.

### SYNOMYS

Hepatoma  
HCC

#### ICD-9CM CODES

155.0 Hepatocellular carcinoma

#### ICD-10CM CODES

C22.0 Liver cell carcinoma

## EPIDEMIOLOGY & DEMOGRAPHICS

Fifth most common cancer worldwide (>500,000 new cases/year) and third most common cause of cancer deaths. Incidence varies worldwide:

- Areas with high rates of hepatitis B and C (Asia, sub-Saharan Africa) have high rates of HCC.
- Males more affected than females, with ratios between 2:1 and 4:1.
- Peak incidence: fifth and sixth decades in Western countries, earlier in areas with perinatal transmission of hepatitis B.
- Incidence rapidly growing in U.S. secondary to chronic hepatitis C infection and obesity leading to nonalcoholic steatohepatitis (NASH).
- 1. Incidence: during the past two decades, the incidence of HCC in the U.S. has tripled. The greatest proportional increase in cases has been among Hispanics and whites between 45 and 60 years of age
- 2. Mean age of diagnosis approximately 65 yr
- 3. HCC is the fastest-rising cause of cancer-related deaths in the United States
- Risk factors:
  1. Chronic hepatitis B infection: accounts for 50% of all cases of HCC and virtually all childhood cases
  2. Chronic hepatitis C infection: markers of HCV infection are found in 80% to 90% of patients with HCC in Japan, 44% to 66% in Italy, and 30% to 50% in the U.S.
  3. Cirrhosis from causes other than viral hepatitis: alcoholic liver disease, nonalcoholic steatohepatitis, primary biliary cirrhosis, hemochromatosis,  $\alpha_1$ -antitrypsin deficiency, and autoimmune hepatitis
  4. Hepatotoxins: alcohol and aflatoxin B1
  5. Systemic diseases affecting the liver such as tyrosinemia
  6. Obesity and diabetes mellitus

## PHYSICAL FINDINGS & CLINICAL PRESENTATION

- One third of patients are asymptomatic. Abdominal pain may be the initial presentation.
- Signs of underlying cirrhosis and portal hypertension are often present.
- Previously compensated cirrhosis with new ascites, encephalopathy, jaundice, or bleeding.
- Paraneoplastic syndromes (hypoglycemia, erythrocytosis, hypercalcemia, severe diarrhea) may be present.

## Dx DIAGNOSIS

### DIFFERENTIAL DIAGNOSIS

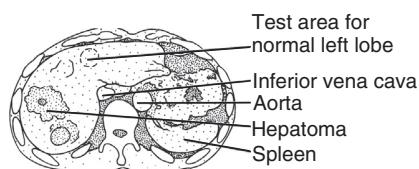
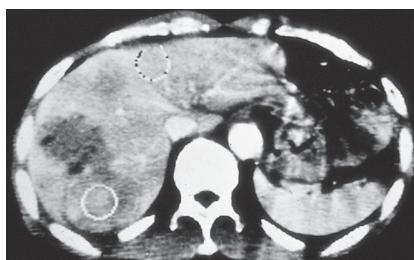
- Metastatic tumor to liver
- Intrahepatic cholangiocarcinoma
- Benign liver tumors such as adenomas, focal nodular hyperplasia, and hemangiomas
- Focal fatty infiltration

### WORKUP

- History regarding risk factors
- Physical examination with attention to signs of chronic liver disease
- Laboratory evaluation and imaging studies
- Imaging studies: ultrasound for initial screening; 4-phase multidetector CT scan or dynamic contrast-enhanced MRI for HCC diagnosis

### LABORATORY TESTS

- Liver function tests
- $\alpha$ -Fetoprotein (AFP) levels can be elevated in 70% of patients (sensitivity, 40% to 65%; specificity, 80% to 94%). An AFP level of 400 ng/ml or greater is highly suggestive of HCC; however, elevations may not be seen in up to 40% of patients with small HCC lesions (<3 cm).



**FIGURE H1-31 Hepatoma.** CT scan shows a diffuse lesion in the right lobe of an otherwise normal liver. (From Skarin AT: *Atlas of diagnostic oncology*, ed 3, St Louis, 2003, Mosby.)



**FIGURE H1-32 HEPATOCELLULAR CARCINOMA.** Laparoscopic view shows a cirrhotic liver with a nodular hepatoma. (From Skarin AT: *Atlas of Diagnostic Oncology*, ed 4, St Louis, 2010, Mosby.)

- Paraneoplastic syndromes associated with HCC may cause hypercalcemia, hypoglycemia, and polycythemia
- Elevated serum HBV DNA level ( $\geq 10,000$  copies/ml) is a strong risk predictor of HCC independent of HBeAg, serum aminotransferase level, and liver cirrhosis

### IMAGING STUDIES

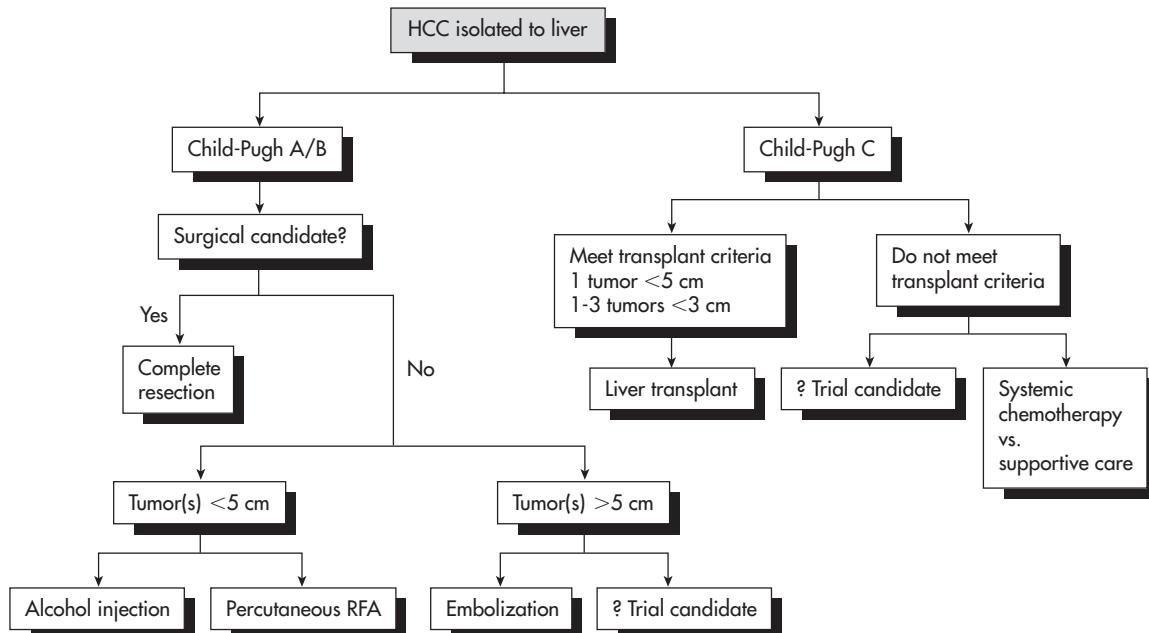
Ultrasound (US), CT scan (Fig. H1-31), or MRI. Ultrasound is most commonly used as a screening test for HCC in high-risk patients every 6 months. Fig. H1-32 shows a laparoscopic view of a cirrhotic liver with a nodular hepatoma.

The following imaging modalities are recommended based on US findings:

- Hepatic lesion <1 cm needs to be followed with a repeat US every 3 months to ensure the lesion does not change in size. If there is no change in size (remains <1 cm) or characteristics after 24 months, the interval for US surveillance can be increased back to every 6 months
- Hepatic lesion >1 cm needs further imaging to confirm the diagnosis of HCC. Either a 4-phase multidetector CT (MDCT) scan or a dynamic contrast-enhanced MR scan is performed. If the chosen imaging modality shows characteristics typical of HCC (hypervascular in the arterial phase with washout in the portal venous or delayed phase) the diagnosis of HCC is confirmed with no need for additional diagnostic testing or biopsy. If the imaging modality is inconclusive or atypical for HCC then the alternate imaging test must be performed (e.g., if the first modality was MRI then the MDCT scan needs to be performed and vice versa). If the second imaging modality is also inconclusive, a biopsy to confirm diagnosis is recommended.

**BIOPSY:** Percutaneous biopsy under ultrasound or CT scan is obtained in the event that imaging studies are nondiagnostic or atypical for HCC, or if no cirrhosis is present. Negative biopsy results should be followed and the hepatic nodule reassessed every 3 to 6 months until it is no longer seen, enlarges, or shows diagnostic characteristics.

**SCREENING:** Screening high-risk patients with US every 6 mo is currently recommended to identify HCC at an early stage. The use of AFP in addition to US is currently under debate; though it does increase detection rate it also



**FIGURE H1-33 Treatment algorithm for hepatocellular carcinoma (HCC).** RFA, Radiofrequency ablation. (From Abeloff MD: *Clinical oncology*, ed 3, Philadelphia, 2004, Saunders.)

**TABLE H1-18 Milan Criteria of Eligibility for Liver Transplantation**

Presence of a tumor ≤5 cm in diameter in patients with single hepatocellular carcinomas  
or  
≤3 tumor nodules, each 3 cm or less in diameter, in patients with multiple tumors

From Cameron JL, Cameron AM: *Current surgical therapy*, ed 10, Philadelphia, 2011, Saunders.

increases false-positive results. The use of AFP alone should be discouraged due to limited sensitivity and specificity. Newer tumor markers are currently under investigation, with plasma microRNA expression the most promising. Patients on transplant waiting lists should be regularly screened for HCC because in the U.S. the development of HCC gives increased priority for liver transplantation. Screening for HCC is recommended in the following groups:

- Hepatitis B carriers (HBsAg positive): Asian males >40 yr, Asian females >50 yr, all cirrhotic hepatitis B carriers, family history of HCC and North American blacks/Africans older than age 20 yr
- Cirrhosis (nonhepatitis B): hepatitis C, alcoholic cirrhosis, hemochromatosis, primary biliary cirrhosis, and possibly  $\alpha_1$ -antitrypsin deficiency, autoimmune hepatitis, and nonalcoholic steatohepatitis

**STAGING:** According to the Barcelona Clinic Liver Cancer (BCLC) staging classification, treatment is determined according to stage:

- Early stage (A): asymptomatic single tumor 5 cm or 3 nodules, each ≤3 cm (known as Milan criteria)
- Intermediate stage (B): patients with tumors that exceed early criteria but do not yet show cancer-related symptoms, vascular invasion, or metastases

- Advanced stage (C): patients with mild cancer-related symptoms and/or vascular invasion or extrahepatic spread
- End-stage (D): patients with advanced, symptomatic disease

## RX TREATMENT

- Fig. H1-33 describes a treatment algorithm for HCC.
- Early stage: curative treatment (surgical resection or liver transplantation). Patients who have a single lesion can be offered surgical resection if they are noncirrhotic or have cirrhosis but still have well-preserved liver function, normal bilirubin, and no significant portal hypertension. Liver transplantation is an effective option for patients with HCC corresponding to the Milan criteria (Table H1-18). Living donor transplantation can be offered for HCC if the waiting time is expected to be long. Local ablation is safe and effective therapy for patients who cannot undergo resection or as a bridge to transplantation. With these options, survival at 5 yr ranges from 50% to 70%.
- Intermediate stage: Transarterial chemoembolization (TACE) is recommended as first-line noncurative therapy for nonsurgical patients with large/multifocal HCC who do not have

vascular invasion or extrahepatic spread. Median survival with this option exceeds 2 yr.

- Advanced stage: sorafenib, an oral multi-kinase inhibitor of the vascular endothelial growth factor receptor (VEGF), the platelet-derived growth factor (PDGF) receptor, and Raf, a serine-threonine kinase, has been shown to improve survival and delay disease progression. The SHARP trial included patients with advanced HCC in Child-Pugh A cirrhosis and showed increased median survival from 7.9 to 10.7 mo.
- End stage: palliative care.

## DISPOSITION

- For unresectable tumors, prognosis is poor; 5-yr survival after surgical resection ranges from 30% to 50%.
- In the U.S. the 5-year overall survival rate for HCC is 10% to 12%.

## REFERRAL

To gastroenterologist for treatment planning

## PEARLS & CONSIDERATIONS

### PREVENTION

- Universal hepatitis B vaccination in children in endemic areas has been shown to decrease the incidence of HCC.
- Treatment of patients with chronic hepatitis B-associated cirrhosis with lamivudine reduces the incidence of HCC. Treatment with entecavir in chronic hepatitis B-HCC can improve hepatic function and MELD score.
- HCC screening is recommended in high-risk patients because curative therapies are available for small and early HCC.

- The expression patterns of microRNAs in liver tissue in patients with HCC differ between men and women. The miR-26 expression status of such patients is associated with survival and response to adjuvant therapy with interferon alfa.
- Several observational studies have suggested that radiofrequency ablation (RFA) may have survival benefits similar to hepatic resection (HR) in cirrhotic patients affected by HCC who are not candidates for liver transplantation.
- Patients diagnosed with HCC with an AFP >1000 are at increased risk for recurrence after transplantation regardless of tumor size.
- Recent trials have shown that among patients with advanced HCC, treatment with sorafenib plus doxorubicin monotherapy

resulted in greater median time to progression-free survival. The degree to which this improvement may represent synergism between sorafenib and doxorubicin remains to be defined.

- There are at least 60 new agents, both TKI (tyrosine kinase inhibitors) and monoclonal antibodies, that are being investigated as targeted therapy for advanced HCC in patients who are intolerant or resistant to sorafenib. The future of therapy for advanced HCC will likely lead to the personalized combination of multiple agents to optimize treatment success.
- SALL4 is a marker for a progenitor subclass of hepatocellular carcinoma with an aggressive phenotype. The absence of SALL4 expression in the healthy adult liver enhances

the potential of SALL4 as a treatment target in hepatocellular carcinoma.<sup>1</sup>

## EBM EVIDENCE

Available at [www.expertconsult.com](http://www.expertconsult.com)

## SUGGESTED READINGS

Available at [www.expertconsult.com](http://www.expertconsult.com)

## RELATED CONTENT

Liver Cancer (Patient Information)

AUTHORS: PRANITH PERERA, M.D., and JEANETTE G. SMITH, M.D.

<sup>1</sup>Yong KJ et al: Oncofetal gene SALL4 in aggressive hepatocellular carcinoma, *N Engl J Med* 368: 2266-2276, 2013.



## EBM EVIDENCE

### Abstract<sup>[1]</sup>

#### Background:

Hepatocellular cancer is diagnosed in over half a million persons worldwide each year. Liver cancer is the fifth most common cancer in men and the seventh in women, with 85% of cases occurring in developing countries, especially where infection with hepatitis B (HBV) is endemic: Southeast Asia and sub-Saharan Africa. Rarely does hepatocellular carcinoma manifest before age 40 years and cases peak at about age 70 years. Infection with hepatitis C virus (HCV) is the fastest-rising cause of cancer-related death in the United States. The 5-year survival of HCV-related cancer is less than 12%. The greatest proportional increase in cases is seen in Hispanics and white persons age 45 to 60 years. Risk factors, diagnosis, treatment, and prevention of hepatocellular carcinoma were investigated.

#### Risk Factors:

The major risk factors for hepatocellular carcinoma are infection with HBV or HCV, alcoholic liver disease, and nonalcoholic fatty liver disease. Less common risk factors are hereditary hemochromatosis, alpha<sub>1</sub>-antitrypsin deficiency, autoimmune hepatitis, some porphyrias, and Wilson's disease. The distribution of risk factors varies by geographic area and race or ethnic group. Usually the risk factors produce cirrhosis, found in 80% to 90% of patients with hepatocellular carcinoma.

Worldwide, chronic HBV infection is seen in about half of all cases and virtually all pediatric cases. Where HBV infection is transmitted from mother to newborn, up to 90% of infected persons have chronic disease, with HBV often incorporated into host DNA. The risk of hepatocellular carcinoma in persons who are positive for hepatitis B surface antigen (HBsAg) is further increased if the individual is male, elderly, infected for a long time, has a family history of hepatocellular carcinoma, was exposed to aflatoxin, uses alcohol or tobacco, is coinfectected with HBV or hepatitis delta virus, has high levels of HBV hepatocellular replication, or is infected with HBV genotype C.

Hepatocellular carcinoma occurs 15 to 20 times more often in persons infected with HCV than those who are not infected. Most of the excess risk is found in those with advanced hepatic fibrosis or cirrhosis. Risk factors for hepatocellular carcinoma in persons infected with HCV include older age at the time of infection, male gender, coinfection with human immunodeficiency virus (HIV) or HBV, and probably diabetes or obesity. Prolonged heavy alcohol use is another strong indicator of higher risk. Coffee drinking may reduce the risk in some areas, such as Japan and southern Europe. It is also related to reduced insulin levels and a lower risk for type 2 diabetes.

#### Diagnosis:

Noninvasive imaging tests, especially at specialized centers, can be used to diagnose hepatocellular carcinoma in persons with cirrhosis and a focal hepatic mass exceeding 2 cm in diameter. Typical imaging shows areas of early arterial enhancement and delayed washout in the venous or delayed phase of four-phase multidetector computed tomography (CT) or in dynamic contrast-enhanced magnetic resonance imaging (MRI). These changes are related to increased vascularity in the carcinoma. Concordant findings on CT and MRI are recommended if the lesions measure 1 to 2 cm in diameter. An alpha-fetoprotein level of 400 ng/mL or higher is also highly predictive of hepatocellular carcinoma. An image-guided biopsy is considered if the focal hepatic mass has atypical features, the CT and MRI findings do not match, or no cirrhosis is present. A negative biopsy result does not rule out malignant disease; the nodule should be reassessed every 3 to 6 months until it disappears, enlarges, or displays diagnostic characteristics. Risk of tumor seeding along the needle track after biopsy is low. It can be hard to measure liver nodules smaller than 1 cm; it is best to monitor them via ultrasonography (US) every 3 to 6 months for 1 to 2 years.

#### Treatment:

Choice of treatment is related to cancer stage, resources available, and level of practitioner expertise. Recommendations for staging-guided treatment use systems such as the Barcelona Clinic Liver Cancer staging and the Child-Pugh system. Genomic analysis is used to identify possible prognostic biomarkers, but requires validation. High serum and tissue levels of vascular endothelial growth factor are significantly associated with poor survival, but the clinical usefulness of this is unclear.

Very early stage disease is difficult to diagnose, but surgical resection at this stage produces an overall survival of 90%. Choice of therapy is dictated by severity of liver dysfunction, extent of portal hypertension, and presence of coexisting conditions. Patients with solitary tumors and no portal hypertension can undergo surgical resection. Patients with early-stage hepatocellular carcinoma are best managed with liver transplantation or, if transplantation is not possible, local ablation. For patients with intermediate-stage cancer the best choice is transarterial chemoembolization (TACE), which improves 2-year survival by 20% to 25% compared to conservative treatment. Radioembolization with yttrium-90 microspheres has been used as palliative treatment for patients with Child-Pugh class A cirrhosis and intermediate-stage disease. Radical therapy is not appropriate for patients with advanced-stage disease. Carefully selected patients may have an increased survival with TACE, but the primary treatment option for these patients is oral sorafenib. Other small molecules being studied for use in these patients include bevacizumab and cetuximab. In the terminal stage of disease, which includes cancer symptoms related to liver failure, vascular involvement, or extrahepatic spread, 1-year survival is less than 10%. None of the treatments mentioned is of benefit.

The clinical effectiveness of antiviral therapy for infection with HBV or HCV and for surveillance and treatment is low. Transplantation, resection, and TACE are not widely used. It is difficult to implement surveillance that requires repeated assessments over relatively short time periods and strategies to ensure prompt recall. The diagnostic evaluation is complicated, and curative treatments are often unavailable or quite costly.

#### Prevention:

All newborns and persons without immunity at high risk for HBV infection should be given HBV vaccine, which is both safe and effective. Antiviral therapy that controls HBV infection in HBsAg-positive patients and that eradicates HCV in patients with viremia may substantially reduce, but does not eliminate, the risk of hepatocellular carcinoma in patients with viral hepatitis. Risk may be reduced by administering either interferon or lamivudine. Persons infected with HCV who do not have cirrhosis and receive interferon-based treatment with a sustained viral response have up to 75% reduction in risk of hepatocellular carcinoma. Maintenance interferon therapy for patients with HCV infection and cirrhosis with no sustained viral response does not reduce the cancer risk. Surveillance is recommended for high-risk patients. One approach is US of the liver and measurement of serum alpha-fetoprotein levels every 6 to 12 months for patients with cirrhosis or advanced hepatic fibrosis regardless of its cause. HBV carriers with or without cirrhosis who are Africans over age 20 years or Asians over age 40 years or who have a family history of hepatocellular carcinoma can also benefit from this approach. Surveillance is not recommended for HCV-infected persons with mild or no hepatic fibrosis. Alpha-fetoprotein levels in serum are inadequate as the only means of surveillance. US has a sensitivity of about 65% and a specificity of over 90% for early detection. CT and MRI are not generally recommended for surveillance because their sensitivity, specificity, and negative and positive predictive values are unknown and because they are expensive and carry risks for radiation exposure, allergic reaction to contrast medium, nephrotoxicity with CT, and nephrogenic fibrosing dermatopathy when gadolinium is used for MRI in patients with renal insufficiency. <sup>A</sup>

#### Evidence-Based Reference

El-Serag HB: Hepatocellular carcinoma, *N Engl J Med* 365:1118–1127, 2011. <sup>A</sup>

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**BASIC INFORMATION****DEFINITION**

Hepatopulmonary syndrome (HPS) is characterized by intrapulmonary vascular dilation in the setting of liver disease causing an increased alveolar-arterial (A-a) gradient.

**SYNOMYS**

HPS

**ICD-9CM CODES**

417.9 Unspecified disease of pulmonary circulation

**ICD-10CM CODES**

I28.9 Disease of pulmonary vessels, unspecified

K76 Other diseases of liver

**EPIDEMIOLOGY & DEMOGRAPHICS**

**PREVALENCE:** Between 5% and 30% of patients with cirrhosis; wide range due to lack of diagnostic criteria.

**PREDOMINANT SEX AND AGE:** There are no data on gender or age prevalence.

**RISK FACTORS:** Can occur with any degree or etiology of liver disease but is more common in patients with established cirrhosis and portal hypertension. There is no clear relationship between severity of hepatic dysfunction and level of hypoxemia. One recent study suggests that HPS is more common in patients with history of viral hepatitis than in patients with alcoholic cirrhosis.

**GENETICS:** There are new data suggesting that genes involved in the regulation of angiogenesis are associated with the risk of HPS.

**PHYSICAL FINDINGS & CLINICAL PRESENTATION**

- Dyspnea.
- Platypnea: worsened dyspnea when sitting upright compared with supine position due to further ventilation-perfusion mismatch.
- Orthodeoxia: decreased  $\text{Pao}_2$  when the patient is sitting upright compared with supine position due to ventilation-perfusion mismatch.
- Spider angiomata seen in high number.
- Signs of severe hypoxemia (e.g., cyanosis and clubbing of the digits).

**ETOLOGY**

Dilation of intrapulmonary arterioles and dilated vascular channels between pulmonary arteries and veins leading to a ventilation-perfusion mismatch and right-to-left shunting (Fig. EH1-34). Research shows that nitric oxide plays a role in vasodilation. The relationship of vasodilation to liver disease is unclear. New areas of research include endothelin-1, which is produced by

proliferating cholangiocytes, pulmonary angiogenesis, and opiate receptors' influence on NO production.

**Dx DIAGNOSIS****DIFFERENTIAL DIAGNOSIS**

- Portopulmonary hypertension.
- Cavopulmonary anastomosis.
- Hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome).
- Chronic lung disease (i.e., COPD or pulmonary fibrosis) with coexisting liver disease.

**WORKUP**

- Diagnosis should be suspected in patients with cirrhosis who develop hypoxemia in absence of other causes (e.g., COPD, thromboembolism).
- Workup includes lab testing and imaging studies (see following), but diagnosis is based on clinical findings.

**LABORATORY TESTS**

- Arterial blood gas at rest, both supine and erect;  $\text{Pao}_2 < 80 \text{ mm Hg}$ .
- Pulmonary function tests will show nonspecific reduction in DLCO.

There is new evidence showing that blood testing for elevated von Willebrand factor antigen is a good screening test for HPS because it is a surrogate marker for endothelial dysfunction.

**IMAGING STUDIES**

- The most effective screening tool is trans-thoracic echocardiogram with bubble study to rule out right-to-left cardiac shunt; microbubble opacification in left atrium shows vasodilation of pulmonary vascular bed.
- Chest x-ray may show nonspecific bibasilar interstitial pattern.
- Scintigraphic perfusion scanning: technetium-99m-labeled albumin found in brain or spleen indicates dilated pulmonary vasculature or cardiac right-to-left shunt.
- Pulmonary angiography rarely used unless there is potential to embolize arteriovenous malformation (AVM).

**Rx TREATMENT**

Ideal treatment would be targeted against pulmonary vasodilation. Most medications have targeted NO production, the activity of NO synthase or endothelin-1, pulmonary angiogenesis, or even bacterial translocation, but no controlled trials exist. Liver transplantation is the only successful treatment, which leads to improvement in gas exchange or complete resolution in gas exchange in the majority of patients. However, severe hypoxemia with  $\text{Pao}_2 < 50$  has been associated with a high posttransplant mortality. Some studies have shown benefit of transjugular

portosystemic shunting, although it is not currently established treatment. Coil embolization in the setting of pulmonary AVMs is another possible area of treatment.

**NONPHARMACOLOGIC THERAPY**

Oxygen to correct hypoxemia;  $\text{Pao}_2$  will partially correct with administration of supplemental  $\text{O}_2$ .

**ACUTE GENERAL Rx**

Correct hypoxemia with supplemental  $\text{O}_2$ .

**CHRONIC Rx**

Liver transplantation is the only successful treatment; the majority of patients show improvement in oxygenation at 1 year post transplant. There are some data showing worse outcomes for patients with severe HPS ( $\text{PaO}_2 < 50\%$ ), but mortality appears to be improving.

**COMPLEMENTARY & ALTERNATIVE MEDICINE**

One study suggested that garlic supplements might decrease A-a gradient in patients with HPS. Studies of diets containing low amount of L-arginine have not shown benefit.

**DISPOSITION**

The diagnosis of HPS confers a poor prognosis. Patients with HPS have high mortality and shorter median survival than other patients with liver disease, even after adjusting for severity of liver disease. According to one natural history study, compared with patients with similar severity of liver disease and comorbidities whose 5-yr survival was estimated at 63%, those patients with the diagnosis of HPS had a 5 yr survival rate of 23%.

**REFERRAL**

- Referral to pulmonologist to help in establishing diagnosis.
- Referral to a liver transplant center.

**PEARLS & CONSIDERATIONS****COMMENTS**

Consider the diagnosis of HPS in patients with cirrhosis who present with dyspnea without signs of pulmonary edema from fluid overload.

**SUGGESTED READINGS**

Available at [www.expertconsult.com](http://www.expertconsult.com).

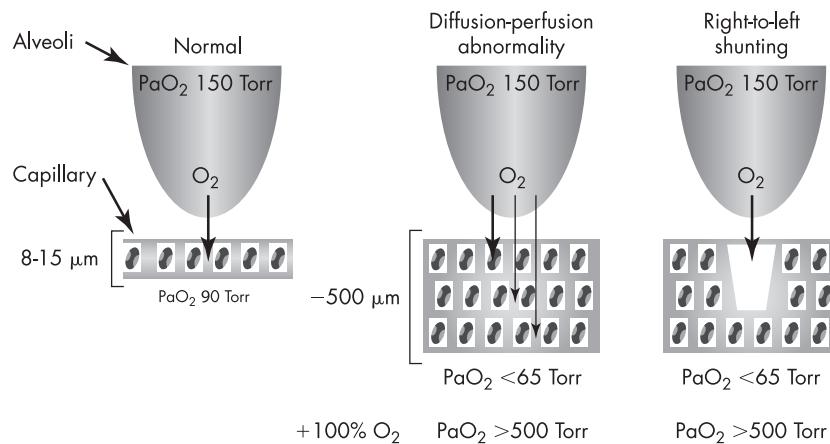
**RELATED CONTENT**

Cirrhosis (Related Key Topic)

AUTHOR: BEVIN KENNEY, M.D.

## SUGGESTED READINGS

- Hoeper MM et al.: Portopulmonary hypertension and hepatopulmonary syndrome, *Lancet* 363:1461, 2004.
- Rodriguez-Roisin R, Krowka MJ: Hepatopulmonary syndrome—a liver-induced lung vascular disorder, *N Engl J Med* 358:2378, 2008.
- Swanson KL et al.: Natural history of hepatopulmonary syndrome: impact of liver transplantation, *Hepatology* 41:1122, 2005.



**FIGURE EH1-34 Pathophysiology of hypoxemia in hepatopulmonary syndrome.** Abnormal intrapulmonary vascular dilation in combination with increased pulmonary blood flow leads to diffusion-perfusion disturbance and arterial hypoxemia, correctable by oxygen supplementation. Most severe intrapulmonary vascular dilation or formation of arteriovenous malformations causes right-to-left shunting only partially correctable by oxygen administration. (From Hoeper MM et al: Portopulmonary hypertension and hepatopulmonary syndrome. *Lancet* 363:1461, 2004.)



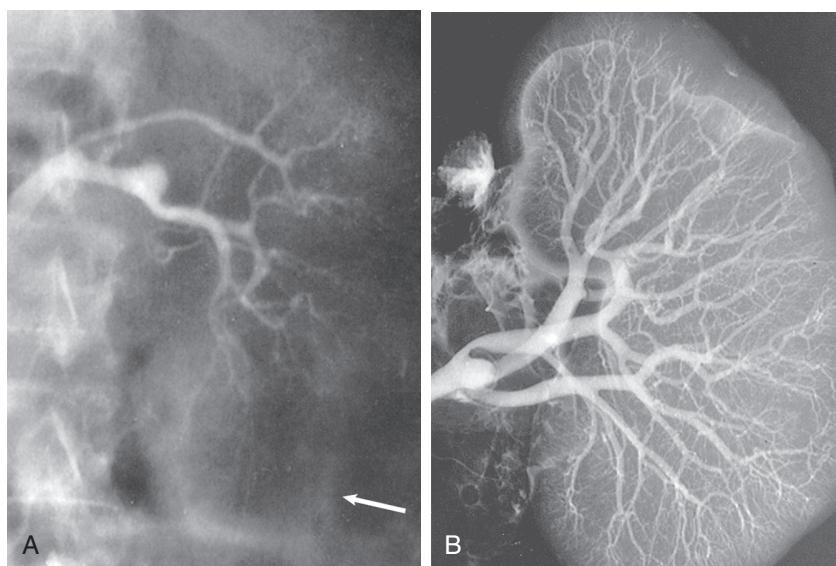
## BASIC INFORMATION

### DEFINITION

Hepatorenal syndrome (HRS) is a condition of intense renal vasoconstriction (see Fig. H1-35) resulting from loss of renal autoregulation occurring as a complication of severe liver disease. Criteria for HRS are:

1. Serum creatinine concentration  $>1.5 \text{ mg/dl}$  or 24-hr creatinine clearance  $<40 \text{ ml/min}$
2. Absence of shock, ongoing infection, and fluid loss and no current treatment with nephrotoxic drugs

3. Absence of sustained improvement in renal function (decrease in serum creatinine to  $<1.5 \text{ mg/dl}$  after discontinuation of diuretics and a trial of plasma expansion)
  4. Absence of proteinuria ( $<500 \text{ mg/day}$ ) or hematuria ( $<50 \text{ red blood cells/high-power field}$ )
  5. Absence of ultrasonographic evidence of obstructive uropathy or parenchymal renal disease
  6. Urinary sodium concentration  $<10 \text{ mmol/L}$
- Tables H1-19 and H1-20** summarize the classic and the revised diagnostic criteria for HRS.



**FIGURE H1-35 Hepatorenal syndrome (HRS).** **A**, Renal angiogram (the arrow marks the edge of the kidney). **B**, The angiogram carried out in the same kidney at autopsy. Note complete filling of the renal arterial system throughout the vascular bed to the periphery of the cortex. The vascular attenuation and tortuosity seen previously (**A**) are no longer present. The vessels are also histologically normal. This indicates the functional nature of the vascular abnormality in HRS. (From Floege J et al: *Comprehensive clinical nephrology*, ed 4, Philadelphia, 2010, Saunders.)

**TABLE H1-19 Diagnostic Criteria for Hepatorenal Syndrome**

#### Major Criteria

- Chronic or acute liver disease with advanced hepatic failure and portal hypertension
- Low glomerular filtration rate, as indicated by serum creatinine  $>1.5 \text{ mg/dl}$  ( $133 \mu\text{mol/L}$ ) or 24-hr creatinine clearance  $<40 \text{ ml/min}$
- Absence of shock, ongoing bacterial infection, and current or recent treatment with nephrotoxic drugs
- Absence of gastrointestinal fluid losses (repeated vomiting or intense diarrhea)
- Absence of renal fluid losses (weight loss  $>500 \text{ g/day}$  for several days in patients with ascites without peripheral edema or  $1000 \text{ g/day}$  in patients with peripheral edema)
- No sustained improvement in renal function (decrease in serum creatinine to  $1.5 \text{ mg/dl}$  [ $135 \mu\text{mol/L}$ ] or less or increase in creatinine clearance to  $40 \text{ ml/min}$  or more) following diuretic withdrawal and expansion of plasma volume with 1.5 liters of isotonic saline
- Proteinuria  $<500 \text{ mg/day}$  and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease

#### Additional Criteria

- Urine volume  $<500 \text{ ml/day}$
- Urine sodium  $<10 \text{ mmol/L}$
- Urine osmolality greater than plasma osmolality
- Urine red blood cells  $<50$  per high-power field
- Serum sodium concentration  $<130 \text{ mmol/L}$

From Floege J et al: *Comprehensive clinical nephrology*, ed 4, Philadelphia, 2010, Saunders.

There are two types of HRS (see Table H1-21):

1. Type 1: progressive impairment in renal function as defined by a doubling of initial serum creatinine  $>2.5 \text{ mg/dl}$  in  $<2 \text{ weeks}$
2. Type 2: stable or slowly progressive impairment of renal function not meeting the above criteria

#### SYNOMYMS

Hepatic nephropathy  
Oliguric renal failure of cirrhosis  
HRS

#### ICD-9CM CODES

572.4 Hepatorenal syndrome

#### ICD-10CM CODES

K76.7 Hepatorenal syndrome

#### EPIDEMIOLOGY & DEMOGRAPHICS

The probability of HRS in patients with cirrhosis is 18% at 1 yr and 39% at 5 yr.

#### PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Evidence of cirrhosis is usually present: jaundice, spider angiomas, splenomegaly, ascites, fetor hepaticus, pedal edema.

**TABLE H1-20 Revised Diagnostic Criteria for Hepatorenal Syndrome**

Cirrhosis with ascites

Serum creatinine  $>1.5 \text{ mg/dl}$  ( $133 \mu\text{mol/L}$ )

No improvement in serum creatinine (decrease to a level of  $1.5 \text{ mg/dl}$ ) after at least 2 days with diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is  $1 \text{ g/kg}$  of body weight per day up to a maximum of  $100 \text{ g/day}$ .

Absence of shock

No current or recent treatment with nephrotoxic drugs

Absence of parenchymal kidney disease as indicated by proteinuria  $>500 \text{ mg/day}$ , microhematuria ( $>50 \text{ red blood cells per high-power field}$ ) and/or abnormal renal ultrasound

From Floege J et al: *Comprehensive clinical nephrology*, ed 4, Philadelphia, 2010, Saunders.

**TABLE H1-21 Definition of Hepatorenal Syndrome Type 1 and Type 2**

#### Type 1 Hepatorenal Syndrome

Doubling of serum creatinine  $>2.5 \text{ mg/dl}$  ( $220 \mu\text{mol/L}$ ) or a 50% reduction in 24-hr creatinine clearance to  $<20 \text{ ml/min}$   $<2 \text{ weeks}$   
Frequently follows a precipitating event (e.g., infection)  
Median survival without treatment: 2 weeks

#### Type 2 Hepatorenal Syndrome

Less rapid renal functional deterioration than type 1  
Mainly presents with refractory ascites  
Median survival without treatment: 4–6 months

From Floege J et al: *Comprehensive clinical nephrology*, ed 4, Philadelphia, 2010, Saunders.

- Hepatic encephalopathy: flapping tremor (asterixis), coma.
- Tachycardia and bounding pulse.
- Oliguria.

### Etiology

An exacerbation of end-stage liver disease, HRS may occur after significant reduction of effective blood volume (e.g., paracentesis, GI bleeding, diuretics) or in the absence of any precipitating factors.

## Dx Diagnosis

### Differential Diagnosis

- Prerenal azotemia: response to sustained plasma expansion is good (prompt diuresis with volume expansion). Volume challenge (to increase mean arterial pressure) followed by large-volume paracentesis (to increase cardiac output and decrease renal venous pressure) may be useful to distinguish HRS from prerenal azotemia in patients with FENa <1%. In patients with prerenal azotemia, the increase in renal perfusion pressure and renal blood flow will result in prompt diuresis; the volume challenge can be accomplished by giving a solution of 100 g of albumin in 500 ml of isotonic saline.
- Acute tubular necrosis: urinary sodium >30 mEq/L, fractional excretion of sodium (FENa) >1.5%, urinary/plasma creatinine ratio <30, urine/plasma osmolality ratio = 1, urine sediment reveals casts and cellular debris, no significant response to sustained plasma expansion.

### Workup

Patients with acute azotemia and oliguria in the setting of liver disease should undergo laboratory evaluation to differentiate HRS from acute tubular necrosis and volume challenge to differentiate HRS from prerenal azotemia if FENa <1%.

### Laboratory Tests

- Obtain serum electrolytes, blood urea nitrogen, creatinine, osmolality, urinalysis, urinary sodium, urinary creatinine, urine osmolality.
- Calculate FENa.
- In HRS: urinary sodium <10 mEq/L, FENa <1%, urinary plasma creatinine ratio >30, urinary plasma osmolality ratio >1.5, urine sediment unremarkable.

### Imaging Studies

Renal ultrasound may be indicated if renal obstruction is suspected.

## Rx Treatment

### Nonpharmacologic Therapy

- Avoidance of precipitating factors.
- Transjugular intrahepatic portosystemic shunts may be effective in selected patients, but data are limited.
- Dialysis with molecular adsorbent recirculating systems remains investigational until more data are available.

### Acute General Rx

- The only effective treatment of HRS is liver transplantation; ornipressin is used in some liver units to avoid further deterioration of renal function in patients awaiting liver transplantation. In general, dopamine and prostaglandins are ineffective in treating patients with HRS.
- The best approach to the management of HRS based on its pathogenesis is the administration of vasoconstrictor drugs (terlipressin, norepinephrine, midodrine). Terlipressin may improve renal perfusion by reversing splanchnic vasodilation, which is the hallmark of HRS. Encouraging results were found in a recent study using continuous IV noradrenalin in combination with albumin and furosemide. In this study, reversal of HRS was achieved in 10 of 12 patients.

- Treatment of HRS with vasoconstrictors for 5 to 15 days in attempt to reduce serum creatinine to <1.5 mg/dL is as follows:
  1. Administration of one of the following drugs or drug combinations:
    - a. Norepinephrine (0.5 to 3.0 mg/hr IV).
    - b. Midodrine (7.5 mg PO tid, increased to 12.5 mg tid if needed) in combination with octreotide (100 micrograms SC tid, increased to tid prn).
    - c. Terlipressin (0.2 to 2.0 mg IV q4 to 12h).
  2. Concomitant administration of albumin (1 g/kg IV on day 1, followed by 20 to 40 g daily)

### Disposition

Mortality rate exceeds 80%; liver transplantation is the only curative treatment.

### Referral

Referral for liver transplantation when indicated (see "Comments").

## Pearls & Considerations

### Comments

Liver transplantation may be indicated in otherwise healthy patients (age preferably <65 yr) with sclerosing cholangitis, chronic hepatitis with cirrhosis, or primary biliary cirrhosis. Contraindications to liver transplantation are AIDS, most metastatic malignancies, active substance abuse, uncontrolled sepsis, and uncontrolled cardiac or pulmonary disease.

### Suggested Readings

Available at [www.expertconsult.com](http://www.expertconsult.com)

### Related Content

Hepatorenal Syndrome (Patient Information)

AUTHOR: FRED F. FERRI, M.D.

## SUGGESTED READINGS

- Duvoux C et al.: Effects of noradrenalin and albumin in patients with type 1 hepatorenal syndrome: a pilot study, *Hepatology* 36:374, 2002.
- Gines P, Schrier RW: Renal failure in cirrhosis, *N Engl J Med* 361:1279–1290, 2009.
- Gines P et al.: Management of cirrhosis and ascites, *N Engl J Med* 350:1646, 2004.



## BASIC INFORMATION

### DEFINITION

Any disorder affecting the peripheral nervous system, including nerve roots, plexuses, and individual peripheral nerves, that has a genetic basis of inheritance and has been or is capable of being transmitted along generations.

There are many different types of hereditary peripheral neuropathies, including Dejerine-Sottas disease, inherited metabolic neuropathies, hereditary sensory and autonomic neuropathies (HSANs), and hereditary motor neuropathies. Most disorders are diagnosed in infancy or childhood; as such, adult clinicians rarely see these patients. For this reason, this chapter discusses only the hereditary motor and sensory neuropathies that an adult clinician might encounter.

### SYNOMYNS

Charcot-Marie-Tooth (CMT) disease, a.k.a. hereditary motor-sensory neuropathy (HMSN). Hereditary neuropathy with liability to pressure-sensitive palsies (HNPP).

#### ICD-9CM CODES

CMT: 356.1

HNPP: 689

#### ICD-10CM CODES

G60.0 Hereditary motor and sensory neuropathy

G60.8 Other hereditary and idiopathic neuropathies

G60.9 Hereditary and idiopathic neuropathy, unspecified

### EPIDEMIOLOGY & DEMOGRAPHICS

All CMT: approximately 30 per 100,000

- CMT type 1 (demyelinating pathophysiology): 1 in 2500
  - CMT type 2 (axonal pathophysiology): 7 in 1000
  - CMT type 4 and CMT-X: rare (either axonal or demyelinating pathophysiology)
- HNPP: 2 to 5 per 100,000

### PHYSICAL FINDINGS & CLINICAL PRESENTATION

CMT: Highly variable

- Age at onset earlier for CMT-1 than CMT-2, but both may present from childhood to old age.
- Severely affected patients have severe distal weakness and muscle atrophy with hand (prominently affecting interossei) and foot deformities (pes cavus, high arched feet, hammer toes).
- Mildly affected patients may have only foot deformity (pes cavus) with little or no weakness/sensory loss.
- Legs can be affected greater than arms, and patients will complain of gait abnormalities (steppage), which cause them to trip and fall.
- Sensory complaints (paresthesias, numbness, dysesthesia) are uncommon despite physical findings of impaired sensation.

- Decreased or absent reflexes.
- Some patients may have postural tremor of the upper limbs.

HNPP (a.k.a. tomaculous neuropathy):

- Age at onset is commonly adolescence.
- Disorder is characterized by recurrent entrapment of peripheral nerves with accompanying signs and symptoms (paresthesias and/or weakness in anatomic distributions). Most common are:
  1. Median nerve at the wrist (carpal tunnel syndrome)
  2. Ulnar nerve at the elbow (cubital tunnel syndrome)
  3. Painless brachial plexopathies
  4. Lateral femoral cutaneous nerve (meralgia paresthetica)
  5. Peroneal nerve at the fibular head
- May be associated with a generalized polyneuropathy.

### ETIOLOGY

CMT: more than 30 subgroups have been identified and have various chromosomal abnormalities.

- Most common mutation is PMP-22 duplication, giving rise to CMT 1A demyelinating phenotype.
- Other mutations include P0 (demyelinating) and neurofilament light chain mutations (demyelinating or axonal phenotype)—see the following.
- Updated information may be available at <http://www.neuro.wustl.edu/neuromuscular>.

## Dx DIAGNOSIS

### DIFFERENTIAL DIAGNOSIS

CMT: other genetic, metabolic, and multisystem disorders including:

- Spinocerebellar ataxias
- Friedreich's ataxia
- Leukodystrophies
- Refsum's disease (elevated serum phytanic acid)
- Distal spinal muscular atrophies and distal myopathies, which can present with pes cavus and other foot deformities
- Chronic inflammatory demyelinating polyneuropathy (CIDP)

HNPP:

- Hereditary neuralgic amyotrophy (HNA), which typically is painful rather than painless. In addition, in HNA, there is no evidence of generalized polyneuropathy.
- Multifocal motor neuropathy with conduction block (MMNCB)—autoimmune-mediated pure motor neuropathy
- Neuropathy associated with renal failure
- Lead neuropathy
- Neuropathy relating to paraproteinemia (demyelinating pathophysiology)

### EVALUATION

CMT

- History of gradual onset symptoms is important to distinguish CMT from other forms of neuropathy.

- Detailed family history with pedigree is essential. Consider examination of multiple family members.

- History should evaluate for potential heavy metal exposure.
- History of dysesthesias is uncommon and should prompt search for acquired neuropathy or other inherited neuropathies (e.g., Fabry's disease).

HNPP: genetic testing after identification of multiple entrapment neuropathies on EMG and nerve conduction studies

### LABORATORY TESTS

- Neurophysiology: electromyography (EMG) and nerve conduction studies (NCSs) must be done first to determine type of pathophysiology: demyelinating or axonal. This will guide genetic testing.

• NCSs in CMT-1 will reveal demyelinating physiology characterized by very slow conduction velocities (around 15 to 30 m/s) with prolonged distal latencies. Inherited demyelinating disorders can be distinguished from acquired demyelinating disorders (e.g., chronic inflammatory demyelinating polyneuropathy or CIDP) by the presence of conduction block in the latter.

- In HNPP, diffusely prolonged distal latencies with superimposed entrapment neuropathies at common sites will be seen on NCSs.
- EMG will reveal reinnervation characterized by long-duration, large-amplitude, polyphasic motor unit potentials (MUPs) with decreased MUP recruitment.

- Genetic tests are available for some CMT subtypes:

1. CMT-1A: chromosome 17p11-PMP-22 duplication
2. CMT-1B: chromosome 1q22-P0 mutation
3. CMT-2E: chromosome 8p21-neurofilament light chain (NF-L) point mutation
4. CMT-X: connexin 32 mutations
5. HNPP: chromosome 17p11 deletion, which includes the PMP-22 gene
- Serum and 24-hour urine levels of heavy metals (arsenic, lead, etc.)
- SPEP, UPEP, immunofixation (for paraprotein).
- Anti-GM1 antibody (positive in ~50% of patients with MMNCB).
- Lumbar puncture may reveal elevated CSF protein in CIDP.
- Peripheral nerve biopsy:
  1. Demyelination with "onion bulb formation." Tomaculae, or focal thickening of myelin sheaths, is seen in HNPP
  2. Generally not indicated unless diagnosis is uncertain

### IMAGING STUDIES

- Spine plain films: for evaluation of scoliosis.
- MRI: indicated if dissociative sensory loss (dorsal column dysfunction with intact spinothalamic tract function) or if upper motor neuron findings (spasticity, Babinski's sign, clonus, increased tendon reflexes) are present.
- Exclusion of involvement of brain or spinal cord compressive lesions causing arm or leg weakness.

- Some inherited peripheral demyelinating disorders (i.e., CMT-X) are associated with intracerebral white matter abnormalities on MRI.
- Exclusion of structural, infectious, or inflammatory nerve root pathology.

## RX TREATMENT

There is no known cure for any of these disorders. Management is supportive.

### NONPHARMACOLOGIC THERAPY

- Physical therapy (PT) and occupational therapy (OT) to provide assistance with gait and coordination.
- PT and OT might provide walking aid such as ankle foot orthosis (AFO), cane, walker, or wheelchair depending on the severity of the neuropathy.
- Wrist splints for superimposed carpal tunnel syndrome.
- Elbow pads (Heelbo Pads) to cushion the ulnar nerve at the elbow.
- Heel-cord strengthening.
- Stretching exercises.
- Analgesics for pain associated with foot deformity.
- Surgical correction of foot deformities by orthopedic surgeons if indicated.  
Vincristine may worsen existing neuropathy (important for oncologist to know if patient develops cancer requiring chemotherapy).

### SURGICAL TREATMENT

- Patients with HNPP should probably not undergo surgical decompression of the median nerve at the wrist or the ulnar nerve at the

elbow; these nerves are sensitive to manipulation. Poor results have been reported with ulnar nerve transposition.

- Anesthesiologists should be aware of HNPP diagnosis in patients undergoing surgery to prevent compression neuropathies from occurring during surgical procedures.

### GENETIC COUNSELING

Must be routinely done for patient and family when diagnosis is established. Many aspects of the patient and family's life are affected, including:

- Future progeny of patient and/or patient's parents or children
- Psychosocial aspects including social functioning, marriage, employment
- Financial needs
- Medical and life insurability

### PROGNOSIS

- CMT: slowly progressive, and patients often remain ambulatory until late in life. Life expectancy is normal. Patients with respiratory involvement (i.e., phrenic nerve involvement with diaphragm paresis) may have shorter life expectancy.
- HNPP: benign prognosis.

### DISPOSITION

Outpatient care. Routine follow-up appointments should be done initially every 6 mo, and then every 1 to 2 yr.

### REFERRAL

- Neurology and/or neuromuscular disease specialist
- Podiatry for recurrent foot problems, including appropriate arches

## PEARLS & CONSIDERATIONS

### PATIENT & FAMILY EDUCATION

Patients can benefit from use of Muscular Dystrophy Association (MDA) resources.

## EBM EVIDENCE

Available at [www.expertconsult.com](http://www.expertconsult.com)

## SUGGESTED READINGS

Available at [www.expertconsult.com](http://www.expertconsult.com)

### RELATED CONTENT

Fig. N1-11 Neuropathic pain, diagnostic approach (Algorithm)  
Charcot-Marie-Tooth Disease (Related Key Topic)

AUTHOR: GAVIN BROWN, M.D.



## EVIDENCE

### Abstract<sup>[1]</sup>

#### Objective:

To improve understanding of TRPV4-associated axonal Charcot-Marie-Tooth (CMT) neuropathy phenotypes and their debated pathologic mechanism.

#### Methods:

A total of 17 CMT2C phenotypic families with vocal cord and diaphragmatic involvement and 36 clinically undifferentiated CMT2 subjects underwent sequencing analysis of the coding region of *TRPV4*. Functional studies of mutant proteins were performed using transiently transfected cells for TRPV4 subcellular localization, basal and stimulated Ca<sup>2+</sup> channel analysis, and cell viability assay with or without channel blockade.

#### Results:

Two *TRPV4* mutations R232C and R316H from 17 CMT2C families were identified in the ankyrin repeat domains. The R316H is a novel de novo mutation found in a patient with CMT2C phenotype. The family with R232C mutation had individuals with and without vocal cord and diaphragm involvement. Both mutant TRPV4 proteins had normal subcellular localization in HEK293 and HeLa cells. Cells transfected with R232C and R316H displayed increased intracellular Ca<sup>2+</sup> levels and reversible cell death by the TRPV channel antagonist, ruthenium red.

#### Conclusion:

*TRPV4* ankyrin domain alterations including a novel de novo mutation cause axonal CMT2. Individuals with the same mutation may have nondistinct CMT2 or have phenotypic CMT2C with vocal cord paresis. Reversible hypercalcemic gain-of-function of mutant TRPV4 instead of loss-of-function appears to be pathologically important. The reversibility of cell death by channel blockade provides an attractive area of investigation in consideration of treatable axonal degeneration. 

### Evidence-Based Reference

Klein CJ et al.: *TRPV4* mutations and cytotoxic hypercalcemia in axonal Charcot-Marie-Tooth neuropathies, *Neurology* 76:887–894, 2011. 

## SUGGESTED READINGS

Chance PF: Genetic evaluation of inherited motor/sensory neuropathy, *Suppl Clin Neurophysiol* 57:228, 2004.

Scott KR, Kothari MJ: Hereditary neuropathies, *Semin Neurol* 25(2):174, 2005.

Washington University Neuromuscular Disease Center. <http://www.neuro.wustl.edu/neuromuscular>.



## BASIC INFORMATION

### DEFINITION

Herpangina is a self-limited upper respiratory tract infection associated with a characteristic vesicular rash on the soft palate.

### SYNOMYS

Vesicular stomatitis

Acute lymphonodular pharyngitis

**ICD-9CM CODES**

074.0 Herpangina

**ICD-10CM CODES**

B08.5 Enteroviral vesicular pharyngitis

**EPIDEMIOLOGY & DEMOGRAPHICS**

**PREDOMINANT SEX:** Male = female.

**PREDOMINANT AGE:** 3 to 10 yr.

**PHYSICAL FINDINGS & CLINICAL PRESENTATION**

- Characterized by ulcerating lesions typically located on the soft palate ([Fig. H1-36](#)).



**FIGURE H1-36 Herpangina with shallow ulcers in the roof of the mouth.** (Courtesy Marshall Guill, M.D. From Goldstein B [ed]: *Practical dermatology*, ed 2, St Louis, 1997, Mosby.)

- Usually fewer than six lesions that evolve rapidly from a diffuse pharyngitis to erythematous macules and subsequently to vesicles that are moderately painful.
- Fever, vomiting, and headache in the first few days of illness but subsiding spontaneously.
- Pharyngeal lesions typical for several more days.

**ETIOLOGY**

- Most cases caused by coxsackie A viruses (A2, A4, A5, A6, A10).
- Occasional cases caused by other enteroviruses (echovirus and enterovirus 71).

**Dx DIAGNOSIS****DIFFERENTIAL DIAGNOSIS**

- Herpes simplex.
- Bacterial pharyngitis.
- Tonsillitis.
- Aphthous stomatitis.
- Hand-foot-mouth disease.

**WORKUP**

Diagnosis is typically based on characteristic lesions on the soft palate.

**LABORATORY TESTS**

Viral and bacterial cultures of the pharynx to exclude herpes simplex infection and streptococcal pharyngitis if the diagnosis is in doubt.

**Rx TREATMENT**

- Give symptomatic treatment for sore throat: saline gargles and analgesics, and encourage oral fluids.
- No antiviral therapy indicated; avoid antibacterial agents because they are ineffective, increase cost, might result in side effects, and promote antibiotic resistance.

**NONPHARMACOLOGIC THERAPY**

Analgesic throat lozenges are helpful in some cases.

**ACUTE GENERAL Rx**

Antipyretics when indicated.

**CHRONIC Rx**

Self-limited infection.

**DISPOSITION**

- Generally, resolution of symptoms within 1 wk.
- Persistence of fever or mouth lesions beyond 1 wk suggestive of an alternative diagnosis (see "Differential Diagnosis").

**REFERRAL**

For consultation with otolaryngologist or infectious disease specialist if the diagnosis is in doubt.

**PEARLS & CONSIDERATIONS****COMMENTS**

Household outbreaks may occur, especially during the summer months.

**SUGGESTED READINGS**

Available at [www.expertconsult.com](http://www.expertconsult.com)

**RELATED CONTENT**

Herpangina (Patient Information)

AUTHOR: GLENN G. FORT, M.D., M.P.H.

## SUGGESTED READINGS

- Chang LY et al.: Outcome of enterovirus 71 infections with or without stage-based management: 1998 to 2002. *Pediatr Infect Dis J* 23(4):327, 2004.
- Chang LY et al.: Transmission and clinical features of enterovirus 71 infections in household contacts in Taiwan, *JAMA* 291(2):222, 2004.
- Stone MS: Viral exanthems, *Dermatol Online J* 9(3):4, 2003.
- Urashima M et al.: Seasonal models of herpangina and hand-foot-mouth disease to simulate annual fluctuations in urban warming in Tokyo, *Jpn J Infect Dis* 56(2):48, 2003.



## BASIC INFORMATION

### DEFINITION

Herpes simplex is a viral infection caused by the herpes simplex virus (HSV). HSV-1 is associated primarily with oral infections, and HSV-2 causes mainly genital infections. However, either type can infect any site. After the primary infection, the virus enters the nerve endings in the skin directly below the lesions and ascends to the dorsal root ganglia, where it remains in a latent stage until it is reactivated.

### SYNOMS

Genital herpes  
Herpes labialis  
Herpes gladiatorum  
Herpes digitalis

#### ICD-9CM CODES

054.10 Genital herpes  
054.9 Herpes labialis

#### ICD-10CM CODES

B00.1 Herpesvirus vesicular dermatitis  
B00.0 Exzema herpeticum  
A60.9 Anogenital herpesviral infection, unspecified  
B00.9 Herpesviral infection, unspecified

### EPIDEMIOLOGY & DEMOGRAPHICS

- More than 85% of adults have serologic evidence of HSV-1 infection. The seroprevalence of adults with HSV-2 in the United States is 25%; however, only approximately 20% of these persons recall having symptoms of HSV infection.
- Most cases of eye or digital herpetic infections are caused by HSV-1.
- Frequency of recurrence of HSV-2 genital herpes is higher than HSV-1 oral labial infection.
- The frequency of recurrence is lowest for oral labial HSV-2 infections.
- The incidence of complications from herpes simplex (e.g., herpes encephalitis) is highest in immunocompromised hosts.
- Male circumcision significantly reduces the incidence of HSV-2.

### PHYSICAL FINDINGS & CLINICAL PRESENTATION

#### Primary infection

- Symptoms occur from 3 to 7 days after contact (respiratory droplets, direct contact).
- Constitutional symptoms include low-grade fever, headache and myalgias, regional lymphadenopathy, and localized pain.
- Pain, burning, itching, and tingling last several hours.
- Grouped vesicles (Fig. H1-37), usually with surrounding erythema, appear and generally ulcerate or crust within 48 hr.
- The vesicles are uniform in size (differentiating it from herpes zoster vesicles, which vary in size). Scattered erosions covered with exudate may be noted on genitals (Fig. EH1-38).
- During the acute eruption the patient is uncomfortable; involvement of lips and inside

of mouth may make it unpleasant for the patient to eat; urinary retention may complicate involvement of the genital area.

- Lesions generally last from 2 to 6 wk and heal without scarring.

#### Recurrent infection:

- Generally caused by alteration in the immune system; fatigue, stress, menses, local skin trauma, and exposure to sunlight are contributing factors.
- The prodromal symptoms (fatigue, burning and tingling of the affected area) last 12 to 24 hr.
- A cluster of lesions generally evolves within 24 hr from a macule to a papule and then vesicles surrounded by erythema; the vesicles coalesce and subsequently rupture within 4 days, revealing erosions covered by crusts.
- The crusts are generally shed within 7 to 10 days, revealing a pink surface.
- The most frequent location of the lesions is on the vermillion border of the lips (HSV-1), the penile shaft or glans penis and the labia (HSV-2), buttocks (seen more frequently in women), fingertips (herpetic whitlow), and trunk (may be confused with herpes zoster).
- Rapid onset of diffuse cutaneous herpes simplex (eczema herpeticum) may occur in certain atopic infants and adults. It is a medical emergency, especially in young infants, and should be promptly treated with acyclovir.
- Herpes encephalitis, meningitis, and ocular herpes can occur in patients with immunocompromised status and occasionally in normal hosts.

### ETIOLOGY

HSV-1 and HSV-2 are both DNA viruses.

## Dx DIAGNOSIS

### DIFFERENTIAL DIAGNOSIS

- Impetigo.
- Behcet's syndrome.
- Coxsackie virus infection.
- Syphilis.
- Stevens-Johnson syndrome.



**FIGURE H1-37 Herpes simplex.** (From Scuderi G [ed]: *Sports medicine: principles of primary care*, St Louis, 1997, Mosby.)

- Herpangina.
- Aphthous stomatitis.
- Varicella.
- Herpes zoster.

### WORKUP

Diagnosis is based on clinical presentation. Laboratory evaluation confirms diagnosis.

### LABORATORY TESTS

- Direct immunofluorescent antibody slide tests provide a rapid diagnosis.
- Viral culture is the most definitive method for diagnosis; results are generally available in 1 or 2 days. The lesions should be sampled during the vesicular or early ulcerative stage; cervical samples should be taken from the endocervix with a swab.
- Tzanck smear is a readily available test that will demonstrate multinucleated giant cells. However, it is not a highly sensitive test.
- Pap smear will detect HSV-infected cells in cervical tissue from women without symptoms.
- Serologic tests for HSV: immunoglobulin (Ig) G and IgM serum antibodies. Antibodies to HSV occur in 50% to 90% of adults. The presence of IgM or a fourfold or greater rise in IgG titers indicates a recent infection (convalescent sample should be drawn 2 to 3 wk after the acute specimen is drawn).

## Rx TREATMENT

- Table H1-22 summarizes antiviral chemotherapy for HSV infection.
- Topical acyclovir, penciclovir, and docosanol are optional treatments for recurrent herpes labialis, but they are less effective than oral treatments.

### DISPOSITION

Most patients recover from the initial episode or recurrences without complications; immunocompromised hosts are at risk for complications (e.g., disseminated herpes simplex infection, herpes encephalitis).

**REFERRAL**

- Hospital admission in patients with herpes encephalitis or herpes meningitis and in immunocompromised hosts with diffuse herpes simplex infection.
- Ophthalmology referral in patients with suspected ocular herpes.

**PEARLS &  
CONSIDERATIONS****COMMENTS**

- Provide patient education regarding transmission of HSV.
- Condom use offers significant protection against HSV-1 infection in susceptible women.
- Patients should be instructed on the use of condoms for sexual intercourse and on

avoiding kissing or sexual intercourse until lesions are crusted.

- Patients should also avoid contact with immunocompromised hosts or neonates while lesions are present.
- Proper handwashing techniques should be explained.
- Patients with herpes gladiatorum (cutaneous herpes in athletes involved in contact sports) should be excluded from participation in active sports until lesions have resolved.
- Many new HSV-2 infections are asymptomatic. Since HSV-2 antibody tests have become commercially available, an increasing number of persons have learned that they have genital herpes through serologic testing. Persons with asymptomatic HSV-2 infection shed virus in the genital tract less frequently than persons with symptomatic infection, but much of the difference is attributable to less frequent genital lesions because generally

lesions are accompanied by frequent viral shedding.

- Suppressive treatment of HSV-2 infection lowers the incidence of genital lesions by 70% to 80%, but cuts the rate of HSV-2 transmission to uninfected partners by only 50%.
- Trials involving investigational herpes simplex vaccine have found it to be effective in preventing HSV-1 genital disease and infection, but not in preventing HSV-2 disease or infection.

**SUGGESTED READINGS**

Available at [www.expertconsult.com](http://www.expertconsult.com)

**RELATED CONTENT**

Genital Herpes (Patient Information)

AUTHOR: FRED F. FERRI, M.D.

**TABLE H1-22** Antiviral Chemotherapy for Herpes Simplex Virus Infection

**Mucocutaneous HSV Infections****Infections in Immunosuppressed Patients**

*Acute symptomatic first or recurrent episodes:* IV acyclovir (5 mg/kg q8h) and oral acyclovir (400 mg qid), famciclovir (500 mg PO tid), or valacyclovir (500 mg PO bid) for 7-10 days are effective. Treatment duration may vary from 7-14 days.

*Suppression of reactivation disease:* IV acyclovir (5 mg/kg q8h), valacyclovir (500 mg PO bid), or oral acyclovir (400-800 mg 3-5 times per day) prevents recurrences during the immediate 30-day post-transplantation period. Longer-term suppression is often used for persons with continued immunosuppression. In bone marrow and renal transplant recipients, valacyclovir 2 g 4 times daily is also effective in preventing CMV infection. Valacyclovir 4 g 4 times daily has been associated with TTP after extended use in HIV-positive persons. In HIV-infected persons, oral famciclovir (500 mg bid) is effective in reducing clinical and subclinical reactivations of HSV-1 and -2.

**Genital Herpes**

*First episodes:* Oral acyclovir (200 mg five times per day or 400 mg tid), oral valacyclovir (1000 mg bid), or famciclovir (250 mg bid) for 10-14 days is effective. IV acyclovir (5 mg/kg q8h for 5 days) is given for severe disease or neurologic complications such as aseptic meningitis.

*Symptomatic recurrent genital herpes:* Oral acyclovir (200 mg 5 times per day for 5 days, 800 mg PO tid for 2 days), valacyclovir (500 mg bid for 3 or 5 days), or famciclovir (125 mg bid for 5 days). All these therapies are effective in shortening lesion duration.

*Suppression of recurrent genital herpes:* Oral acyclovir (200-mg capsules bid or tid, 400 mg bid, or 800 mg qd), famciclovir (250 mg bid), or valacyclovir (500 mg or 1000 mg qd or 500 mg bid) prevents symptomatic reactivation. Persons with frequent reactivation (<9 episodes/year) can take 500 mg daily; those with >9 episodes/year should take 1000 mg daily or 500 mg bid.

**Oral-Labial HSV Infections**

*First episode:* Oral acyclovir (200 mg) is given 4 or 5 times per day. Famciclovir (250 mg bid) or valacyclovir (1000 mg bid) has been used clinically.

*Recurrent episodes:* Valacyclovir 1000 mg bid for 1 day or 500 mg bid for 3 days is effective in reducing pain and speeding healing. Self-initiated therapy with six times daily topical 1% penciclovir cream is effective in speeding the healing of oral-labial HSV; topical acyclovir cream has also been shown to speed healing.

*Suppression of reactivation of oral-labial HSV:* Oral acyclovir (400 mg bid), if started before exposure and continued for the duration of exposure (usually 5-10 days), prevents reactivation of recurrent oral-labial HSV infection associated with severe sun exposure.

**Herpetic Whitlow**

Oral acyclovir (200 mg) 5 times daily for 7-10 days.

**HSV Proctitis**

Oral acyclovir (400 mg five times per day) is useful in shortening the course of infection. In immunosuppressed patients or in patients with severe infection, IV acyclovir (5 mg/kg q8h) may be useful.

**Herpetic Eye Infections**

In acute keratitis, topical trifluorothymidine, vidarabine, idoxuridine, acyclovir, penciclovir, and interferon are all beneficial. Debridement may be required; topical steroids may worsen disease.

**CNS HSV Infections**

*HSV encephalitis:* Intravenous acyclovir (10 mg/kg q8h; 30 mg/kg per day for 14-21 days is preferred.

*HSV aseptic meningitis:* No studies of systemic antiviral chemotherapy exist. If therapy is to be given, IV acyclovir (15-30 mg/kg/day) should be used.

*Autonomic radiculopathy:* No studies are available.

**Neonatal HSV infections:** Acyclovir (60 mg/kg/day, divided into three doses) is given. The recommended duration of treatment is 21 days. Monitoring for relapse should be undertaken, and some authorities recommend continued suppression with oral acyclovir suspension for 3 to 4 mo.

**Visceral HSV Infections**

*HSV esophagitis:* IV acyclovir (15 mg/kg per day). In some patients with milder forms of immunosuppression, oral therapy with valacyclovir or famciclovir is effective.

*HSV pneumonitis:* No controlled studies exist. IV acyclovir (15 mg/kg per day) should be considered.

**Disseminated HSV infections:** No controlled studies exist. Intravenous acyclovir (10 mg/kg q8h) nevertheless should be tried. No definite evidence indicates that therapy decreases the risk of death.

**Erythema multiforme-associated HSV:** Anecdotal observations suggest that oral acyclovir (400 mg bid or tid) or valacyclovir (500 mg bid) suppresses erythema multiforme.

**Surgical prophylaxis:** Several surgical procedures such as laser skin resurfacing, trigeminal nerve root decompression, and lumbar disk surgery have been associated with HSV reactivation. Intravenous acyclovir (3 mg/kg) and oral acyclovir 800 mg bid, valacyclovir 500 mg bid, or famciclovir 250 mg bid is effective in reducing reactivation. Therapy should be initiated 48 hours before surgery and continued for 3-7 days.

**Infections with acyclovir-resistant HSV:** Foscarnet (40 mg/kg IV q8h) should be given until lesions heal. The optimal duration of therapy and the usefulness of its continuation to suppress lesions are unclear. Some patients may benefit from cutaneous application of trifluorothymidine or 5% cidofovir gel.

## SUGGESTED READINGS

- Belshe RB et al.: Efficacy results of a trial of a herpes simplex vaccine, *N Engl J Med* 366:34–43, 2012.
- Corey L, Wald A: Maternal and neonatal herpes simplex virus infections, *N Engl J Med* 361:1376–1385, 2009.
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- Usatine RP, Tinitigan R: Non-genital herpes simplex virus, *Am Fam Physician* 82(9):1075–1082, 2010.



**FIGURE EH1-38 Primary herpes simplex. A,** Scattered erosions covered with exudate. **B,** Numerous erosions appeared 4 days after contact with an asymptomatic carrier. (From Habif TP: *Clinical dermatology*, ed 4, Philadelphia, 2004, Mosby.)



## BASIC INFORMATION

### DEFINITION

Herpes zoster is a disease caused by reactivation of the varicella-zoster virus, with spread of the virus alone from the sensory nerve to the dermatome. After the primary infection (chickenpox), the virus becomes latent in the dorsal root ganglia and reemerges when there is a weakening of the immune system (as a result of disease or advanced age).

### SYNOMYS

Shingles  
HZ

#### ICD-9CM CODES

053.9 Herpes zoster

#### ICD-10CM CODES

B02 Herpes zoster

B02.7 Disseminated zoster

B02.8 Zoster with other complications

B02.9 Zoster without complications

### EPIDEMIOLOGY & DEMOGRAPHICS

- Herpes zoster occurs during the lifetime of 10% to 20% of the population.
- There is an increased incidence in immunocompromised patients (AIDS, malignancy), the elderly, and children who acquired chickenpox when younger than 2 mo.

### PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Pain generally precedes skin manifestation by 3 to 5 days and is generally localized to the dermatome that will be affected by the skin lesions.
- Constitutional symptoms are often present (malaise, fever, headache).
- The initial rash consists of erythematous maculopapules generally affecting one dermatome (thoracic region in majority of cases [Fig. H1-39]). Typically the rash does not cross the midline. Some patients (<30%) may have scattered vesicles outside the affected dermatome. In rare cases the rash can be generalized (Fig. H1-40).
- The initial maculopapules evolve into vesicles and pustules by the third or the fourth day.
- The vesicles have an erythematous base (Fig. EH1-41), are cloudy, and have various sizes (a distinguishing characteristic from herpes simplex, in which the vesicles are of uniform size) and may have a classic appearance of grouped vesicles (Fig. H1-42).
- The vesicles subsequently become umbilicated and then form crusts that generally fall off within 3 wk; scarring may occur.
- Pain during and after the rash is generally significant. Post-herpetic neuralgia occurs after herpes zoster in approximately one third of patients aged 60 years and older and can persist for months or years.
- Secondary bacterial infection with *Staphylococcus aureus* or *Streptococcus pyogenes* may occur.
- Regional lymphadenopathy may occur.

- Herpes zoster may involve the trigeminal nerve (most frequent cranial nerve involved); involvement of the geniculate ganglion can cause facial palsy and a painful ear, with the presence of vesicles on the pinna and external auditory canal (Ramsay Hunt syndrome).

### ETIOLOGY

Reactivation of varicella virus (human herpes virus III)

## Dx DIAGNOSIS



**FIGURE H1-39** **A** and **B**, Herpes zoster lesions in T3 distribution. (From Swartz, MH: *Textbook of physical diagnosis*, 7th ed, Philadelphia, 2014, Saunders.)



**FIGURE H1-40** Herpes zoster, generalized. (From Swartz, MH: *Textbook of physical diagnosis*, 7th ed, Philadelphia, 2014, Saunders.)

### DIFFERENTIAL DIAGNOSIS

- Rash: herpes simplex and other viral infections
- Pain from herpes zoster: may be confused with acute myocardial infarction, pulmonary embolism, pleuritis, pericarditis, renal colic

### LABORATORY TESTS

Laboratory tests are generally not necessary (viral cultures and Tzanck smear will confirm diagnosis in patients with atypical presentation).

## Rx TREATMENT

### NONPHARMACOLOGIC THERAPY

- Wet compresses (using Burow's solution or cool tap water) applied for 15 to 30 min five to 10 times a day are useful to break vesicles and remove serum and crust.
- Care must be taken to prevent any secondary bacterial infection.

### ACUTE GENERAL Rx

- Oral antiviral agents can decrease acute pain, inflammation, and vesicle formation when treatment is begun within 48 hr of onset of rash. Treatment options are:
  1. Valacyclovir 1000 mg tid for 7 days
  2. Famciclovir 500 mg tid for 7 days
  3. Acyclovir 800 mg 5 times daily for 7 to 10 days
- Corticosteroids should be considered in older patients within 72 hr of clinical presentation or if new lesions are still appearing if there are no contraindications. Initial dose is prednisone 40 mg/day decreased by 5 mg/day until finished. When used there is a decrease in the use of analgesics and time to resumption of usual activities, but there is no effect on the incidence and duration of postherpetic neuralgia.
- Immunocompromised patients should be treated with IV acyclovir 500 mg/m<sup>2</sup> or 10 mg/kg q8h in 1-hr infusions for 7 days, with close monitoring of renal function and adequate hydration; vidarabine (continuous 12-hr infusion of 10 mg/kg/day for 7 days) is also effective for treatment of disseminated herpes zoster in immunocompromised hosts.
- Patients with AIDS and transplant recipients may develop acyclovir-resistant varicella-zoster; these patients can be treated with foscarnet (40 mg/kg IV q8h) continued for at least 2 weeks.



**FIGURE H1-42** Herpes zoster. Classic appearance of grouped vesicles. (From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text*, ed 2, St Louis, 2006, Mosby.)

least 10 days or until lesions are completely healed.

- Postherpetic neuralgia (Fig. EH1-43)
  1. Gabapentin 100 to 600 mg tid is effective in the treatment of pain and sleep interference associated with postherpetic neuralgia. Other effective agents are pregabalin, duloxetine, and tricyclic antidepressants.
  2. Lidocaine patch 5% is also effective in relieving postherpetic neuralgia. Patches are applied to intact skin after resolution of blisters and crusts to cover the most painful area for up to 12 hr within a 24-hr period.
  3. Capsaicin cream can be useful for treatment of postherpetic neuralgia. It is generally applied 3 to 5 times daily for several weeks after the crusts have fallen off. A topical 8% patch formulation of capsaicin is now available by prescription for postherpetic neuralgia.
  4. Sympathetic blocks (stellate ganglion or epidural) with 0.25% bupivacaine and rhizotomy are reserved for severe cases unresponsive to conservative treatment.

#### **DISPOSITION**

- The incidence of postherpetic neuralgia (defined as pain that persists more than

90 days after onset of rash) increases with age (<30% by age 40 yr, >70% by age 70 yr); antivirals reduce the risk of postherpetic neuralgia.

- Incidence of disseminated herpes zoster is increased in immunocompromised hosts (e.g., 15% to 50% of patients with active Hodgkin's disease).
- Immunocompromised hosts are also more prone to neurologic complications (encephalitis, myelitis, cranial and peripheral nerve palsies, acute retinal necrosis). The mortality rate is 10% to 20% in immunocompromised hosts with disseminated zoster.
- Motor neuropathies occur in 5% of all cases of zoster; complete recovery occurs in >70% of patients.
- Rates of HZ recurrence are more frequent than previously reported and are comparable to rates of first HZ occurrence in immunocompetent individuals.

#### **REFERRAL**

- Hospitalization for IV acyclovir in patients with disseminated herpes zoster.
- Patients with herpes zoster ophthalmicus should be referred to an ophthalmologist.
- Vaccination: In the absence of the herpes zoster vaccine, persons who live to 85 yr

of age have a 50% risk of herpes zoster. Immunocompetent adults ≥60 yr are appropriate candidates for a single dose of varicella-zoster vaccine (VZV) whether or not they have had a previous episode of herpes zoster. Immunization with VZV (Zostavax) boosts waning immunity in older adults and reduces the severity and duration of pain caused by herpes zoster by 61%. Adults who are VZV seronegative (never had varicella) should be immunized against varicella with two doses of varicella vaccine (Varivax). Despite its efficacy and safety, use of this vaccine remains low (<8% of potential recipients).



#### **EVIDENCE**

Available at [www.expertconsult.com](http://www.expertconsult.com)

#### **SUGGESTED READINGS**

Available at [www.expertconsult.com](http://www.expertconsult.com)

#### **RELATED CONTENT**

Shingles (Patient Information)

AUTHOR: FRED F. FERRI, M.D.



## EVIDENCE

### Abstract<sup>[1]</sup>

#### Objective:

To present population-based estimates of herpes zoster (HZ) recurrence rates among adults.

#### Patients and Methods:

To identify recurrent cases of HZ, we reviewed the medical records (through December 31, 2007) of all Olmsted County, Minnesota, residents aged 22 years or older who had an incident case of HZ between January 1, 1996, and December 31, 2001. Kaplan-Meier curves and Cox regression models were used to describe recurrences by age, immune status, and presence of prolonged pain at the time of the incident HZ episode.

#### Results:

Of the 1669 persons with a medically documented episode of HZ, 95 had 105 recurrences (8 persons with >1 recurrence) by December 31, 2007, an average follow-up of 7.3 years. The Kaplan-Meier estimate of the recurrence rate at 8 years was 6.2%. With a maximum follow-up of 12 years, the time between HZ episodes in the same person varied from 96 days to 10 years. Recurrences were significantly more likely in persons with zoster-associated pain of 30 days or longer at the initial episode (hazard ratio, 2.80; 95% confidence interval, 1.84-4.27;  $P<.001$ ) and in immunocompromised individuals (hazard ratio, 2.35; 95% confidence interval, 1.35-4.08;  $P=.006$ ). Women and anyone aged 50 years or older at the index episode also had a greater likelihood of recurrence.

#### Conclusion:

Rates of HZ recurrence appear to be comparable to rates of first HZ occurrence in immunocompetent individuals, suggesting that recurrence is sufficiently common to warrant investigation of vaccine prevention in this group. **A**

### Evidence-Based Reference

Yawn BP et al.: Herpes zoster recurrences more frequent than previously reported, *Mayo Clin Proc* 86:88-93, 2011. **A**

## SUGGESTED READINGS

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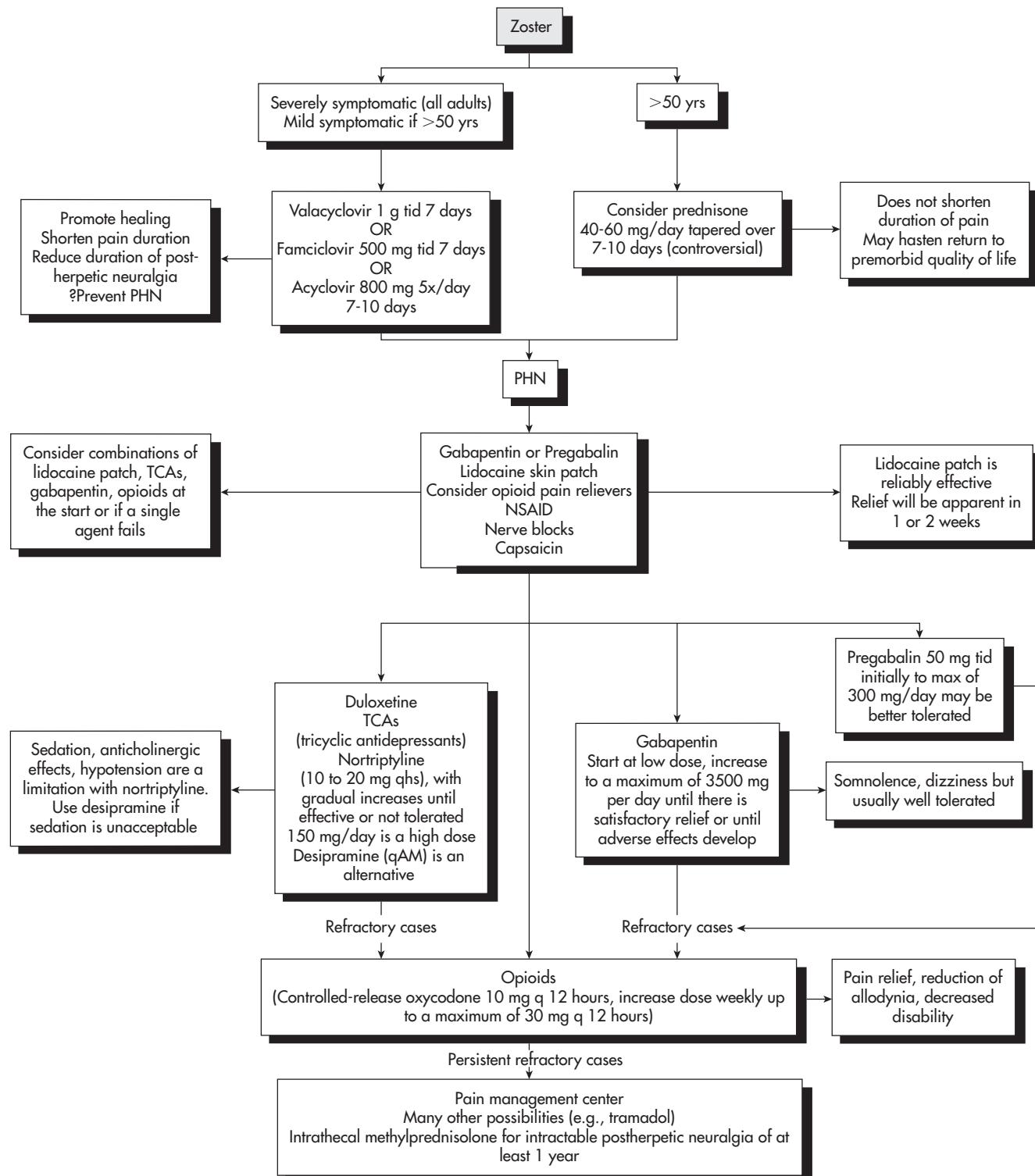
Kimberlin DW, Whitley RJ: Varicella-zoster vaccine for the prevention of herpes zoster, *N Engl J Med* 356:1338, 2007.

Tseng HF et al.: Herpes zoster vaccine in older adults and the risk of subsequent herpes zoster disease, *JAMA* 305(2):160-166, 2011.

Yawn B et al.: Herpes zoster recurrences more frequent than previously reported, *Mayo Clin Proc* 86(2):88-93, 2011.



**FIGURE EH1-41 Herpes zoster occurred in this 3-year-old.** She had chickenpox at age 18 months. The varicella-zoster virus causes both conditions. Spontaneous resolution can be expected. (From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text*, ed 2, St Louis, 2006, Mosby.)



**FIGURE EH1-43 Treatment of herpes zoster and postherpetic neuralgia.** NSAID, Nonsteroidal anti-inflammatory drug; PHN, postherpetic neuralgia. (Modified from Habif TA: *Clinical dermatology*, ed 4, St Louis, 2004, Mosby.)



## BASIC INFORMATION

### DEFINITION

A hiatal hernia is the protrusion of a portion of the stomach into the thoracic cavity through the diaphragmatic esophageal hiatus.

### SYNOMYS

Hiatus hernia

Diaphragmatic hernia

### ICD-9CM CODES

- 553.3 Diaphragmatic hernia without obstruction or gangrene
  - 750.6 Congenital hiatal hernia
  - 756.6 Congenital diaphragmatic hernia
- ### ICD-10CM CODES
- K44.9 Diaphragmatic hernia without obstruction or gangrene
  - Q40.1 Congenital hiatus hernia
  - Q79.0 Congenital diaphragmatic hernia

### EPIDEMIOLOGY & DEMOGRAPHICS

- Found in 50% of patients older than 50 yr.
- Prevalence increases with age.
- More prevalent in Western countries than in Africa and Asia.
- Paraesophageal hiatal hernias are more common in women than in men (4:1).
- Associated with diverticulosis (25%), esophagitis (25%), duodenal ulcers (20%), and gallstones (18%).
- More than 90% of patients with endoscopic documentation of esophagitis have hiatal hernias.

### PHYSICAL FINDINGS & CLINICAL PRESENTATION

Most patients are asymptomatic. If symptoms are present, they resemble those of gastroesophageal reflux disease (GERD).

- Heartburn.
- Dysphagia.
- Regurgitation of gastric contents.
- Chest pain.
- Postprandial fullness.
- GI bleed.
- Dyspnea.
- Hoarseness.
- Wheezing with bowel sounds heard over the left lung base.

### ETIOLOGY

- The repetitive stretching of the gastroesophageal (GE) junction with swallowing and actions (e.g., vomiting) or states (e.g., obesity, pregnancy) that increase intraabdominal pressure may cause widening of the hiatus, rupture of the phrenoesophageal ligament, and onset of the hernia.
- Hiatal hernias are classified as:
  1. Type I: Sliding (Fig. H1-44A), axial, or concentric hiatal hernia (most common type, 99%). Only the GE junction protrudes into the thoracic cavity and the phrenoesophageal ligament remains intact.

2. Type II: Paraesophageal or rolling hernia (Fig. H1-44B) (1%). The GE junction stays at the level of the diaphragm, but part of the stomach bulges into the thoracic cavity through a defect in the phrenoesophageal ligament.
3. Type III: Mixed (rare), a combination of type I and type II.
4. Type IV: Large defect in hiatus that allows other intraabdominal organs to enter the hernia sac.

## Dx DIAGNOSIS

### DIFFERENTIAL DIAGNOSIS

- Peptic ulcer disease.
- Unstable angina.
- Esophagitis (caused by *Candida*, herpes, NSAIDs, etc.).
- Esophageal spasm.
- Barrett's esophagus.
- Schatzki's ring.
- Achalasia.
- Zenker's diverticulum.
- Esophageal cancer.

### WORKUP

- Exclude conditions noted in the differential diagnosis and document the presence of a hiatal hernia. Upper endoscopy may also be needed to exclude abnormal metaplasia, dysplasia, or neoplasia.

### LABORATORY TESTS

- Blood tests are not specific.
- Esophageal manometry, although not commonly done, can be used in establishing a diagnosis (low sensitivity, but high specificity when compared with endoscopy).

### IMAGING

- Upper gastrointestinal (UGI) barium contrast swallow series: best defines the anatomic abnormality. Demonstration that the gastric cardia is herniated 2 cm above the hiatus is diagnostic. UGI may also reveal a tortuous esophagus (Fig. H1-45). If endoscopy is performed preoperatively, a barium swallow is generally not necessary.

- UGI endoscopy: documents the presence of a hiatal hernia and also excludes commonly associated findings of esophagitis and Barrett's esophagus (recommended at least once during the workup). The >2 cm of gastric rugal fold seen above the margins of the diaphragmatic crura is diagnostic.
- Abdominal ultrasonography: simple, well tolerated. A transdiaphragmatic esophageal diameter of more than or equal to 18 mm is highly suggestive of the presence of a sliding hiatal hernia.

## Rx TREATMENT

### NONPHARMACOLOGIC THERAPY

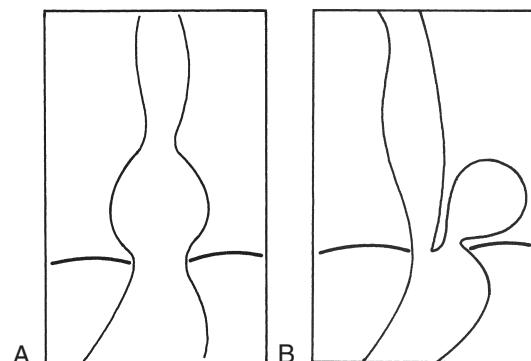
- Lifestyle modifications: avoid foods and drugs that decrease lower-esophageal pressure (e.g., caffeine, chocolate, mint, calcium channel blockers, and anticholinergics).
- Weight loss.
- Avoid large quantities of food with meals.
- Sleep with the head of the bed elevated 6 inches.

### ACUTE GENERAL Rx

- Antacids may be useful to relieve mild symptoms.
- H<sub>2</sub> antagonists (e.g., cimetidine 400 mg bid, ranitidine 150 mg bid, or famotidine 20 mg bid).
- If significant GERD is present with documented esophagitis, proton pump inhibitors (e.g., omeprazole 20 mg qd or lansoprazole 30 mg qd) are used. Refractory symptoms may require higher doses (e.g., bid dosing).
- Prokinetic agents (e.g., metoclopramide 10 mg taken 30 min before each meal) can be added to an H<sub>2</sub> antagonist or proton pump inhibitor.

### CHRONIC Rx

- When indicated, surgery (laparoscopic or open) can be done in patients with refractory symptoms impairing quality of life, or causing intestinal (e.g., recurrent GI bleeds) or extraintestinal complications (e.g., aspiration pneumonia, asthma, or ear-nose-throat complications).



**FIGURE H1-44 Types of esophageal hiatal hernia. A,** Sliding hiatal hernia, the most common type. **B,** Paraesophageal hiatal hernia. (From Behrman RE: *Nelson textbook of pediatrics*, ed 17, Philadelphia, 2004, Saunders.)

- Prophylactic surgery is a consideration in all paraesophageal hernias because they have a higher incidence of strangulation.

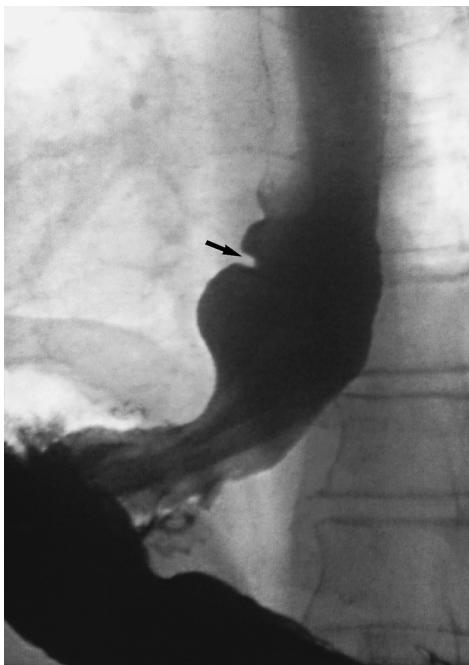
#### **DISPOSITION**

- More than 90% of patients having GERD symptoms respond well to medical therapy.
- Complications of hiatal hernias are similar to complications occurring in patients with GERD:
  1. Erosive esophagitis.
  2. Ulcerative esophagitis.

3. Barrett's esophagus.
4. Peptic stricture.
5. GI hemorrhage.
6. Extraintestinal complications.
7. Lung collapse or heart failure (severe cases).

#### **REFERRAL**

Gastroenterologist: for symptoms refractory to conventional therapy ( $H_2$  antagonists, antacids, and proton pump inhibitors) or having complications previously mentioned.



**FIGURE H1-45** A sliding hiatal hernia confirmed by the presence of an incisural notch (arrow) on the greater curve aspect. (From Grainger RG et al [eds]: *Grainger & Allison's diagnostic radiology*, ed 4, Philadelphia, 2001, Churchill Livingstone.)

#### **PEARLS & CONSIDERATIONS**

##### **COMMENTS**

- Gastric ulceration and erosions (*Cameron's lesion*) can occur in the paraesophageal hernia pouch and are an uncommon cause of UGI bleeding.
- May cause iron deficiency anemia.
- Gastric volvulus or torsion can also occur and presents as dysphagia and postprandial pain.
- High incidence of esophagitis even after the eradication of *Helicobacter pylori*.
- The appearance of hiatal hernia may resemble a left atrial mass by echocardiography.

#### **EBM EVIDENCE**

Available at [www.expertconsult.com](http://www.expertconsult.com)

#### **SUGGESTED READINGS**

Available at [www.expertconsult.com](http://www.expertconsult.com)

#### **RELATED CONTENT**

Hiatal Hernia (Patient Information)

AUTHOR: MARK F. BRADY, M.D., M.P.H., M.M.S.



## EVIDENCE

### Abstract<sup>[1]</sup>

#### Objective and Background:

We lack long-term data (>10 years) on the efficacy of antireflux surgery when evaluated within the framework of randomized clinical trials. Hereby we report the outcome of a randomized trial comparing open total (I) and a Toupet posterior partial fundoplication (II) performed between 1983 and 1991.

#### Methods:

A group of 137 patients with gastroesophageal reflux disease were enrolled into the study. The mean follow up has now reached 18 years. During these years 26% had died and 16% were unable to trace for follow up. Symptom outcomes were assessed by the use of validated self-reporting questionnaires.

#### Results:

Long-term control of heartburn and acid regurgitation (reported as no or mild symptoms) were reported by 80% and 82% after a total fundoplication (I) and corresponding figures were 87% and 90% after a partial posterior fundoplication (II), respectively (n.s.).

The dysphagia scores were low  $4.6 \pm 1.3$  (SEM) in group I and  $3.3 \pm 0.9$  (SEM) in group II (n.s.). The point prevalences of rectal flatulence and gas distension related complaints were of similar magnitude in the 2 groups. Of the total number of patients in the fundoplication group, 23% noted some ability to vomit compared with 31% in the partial posterior fundoplication group.

#### Conclusions:

Both a total and a partial posterior fundoplication maintain a high level of reflux control after 2 decades of follow up. The previously reported differences in mechanical side effects, in favor of the partial wrap, seemed to disappear over time. **A**

### Abstract<sup>[2]</sup>

#### Background:

In 2006, we reported results of a randomized trial of laparoscopic paraesophageal hernia repair (LPEHR), comparing primary diaphragm repair (PR) with primary repair buttressed with a biologic prosthesis (small intestinal submucosa [SIS]). The primary endpoint, radiologic hiatal hernia (HH) recurrence, was higher with PR (24%) than with SIS buttressed repair (9%) after 6 months. The second phase of this trial was designed to determine the long-term durability of biologic mesh-butressed repair.

#### Methods:

We systematically searched for the 108 patients in phase I of this study to assess current clinical symptoms, quality of life (QOL) and determine ongoing durability of the repair by obtaining a follow-up upper gastrointestinal series (UGI) read by 2 radiologists blinded to treatment received. HH recurrence was defined as the greatest measured vertical height of stomach being at least 2 cm above the diaphragm.

#### Results:

At median follow-up of 58 months (range 42 to 78 mo), 10 patients had died, 26 patients were not found, 72 completed clinical follow-up (PR, n=39; SIS, n=33), and 60 repeated a UGI (PR, n=34; SIS, n=26). There were 20 patients (59%) with recurrent HH in the PR group and 14 patients (54%) with recurrent HH in the SIS group ( $p=0.7$ ). There was no statistically significant difference in relevant symptoms or QOL between patients undergoing PR and SIS buttressed repair. There were no strictures, erosions, dysphagia, or other complications related to the use of SIS mesh.

#### Conclusions:

LPEHR results in long and durable relief of symptoms and improvement in QOL with PR or SIS. There does not appear to be a higher rate of complications or side effects with biologic mesh, but its benefit in reducing HH recurrence diminishes at long-term follow-up (>5 years postoperatively) or earlier. **A**

## Evidence-Based References

Mardani J et al.: Total or posterior partial fundoplication in the treatment of GERD: results of a randomized trial after 2 decades of follow-up, *Ann Surg* 253:875–878, 2011. **A**

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## BASIC INFORMATION

### DEFINITION

Hidradenitis suppurativa (HS) is a chronic, relapsing suppurative cutaneous disease affecting skin that bears apocrine glands and manifested by abscesses, fistulating sinus tracts, and chronic infection leading to scarring.

### SYNOMYMS

Acne inversa  
Apocrinitis  
Verneuil's disease

#### ICD-9CM CODES

705.83 Hidradenitis

#### ICD-10CM CODES

L73.2 Hidradenitis suppurativa

### EPIDEMIOLOGY & DEMOGRAPHICS

Onset is postpubertal, with an average age of onset of 23 yr; rates decline after age 55 yr.

**PREVALENCE:** Overall prevalence in the United States is ~1% to 2%.

**PREDOMINANT SEX:** Female to male ratio is 3:1.

### RISK FACTORS

- Obesity and metabolic syndrome.
- Family history (approximately 30%).
- Hyperandrogenism in women.
- Cigarette smoking.

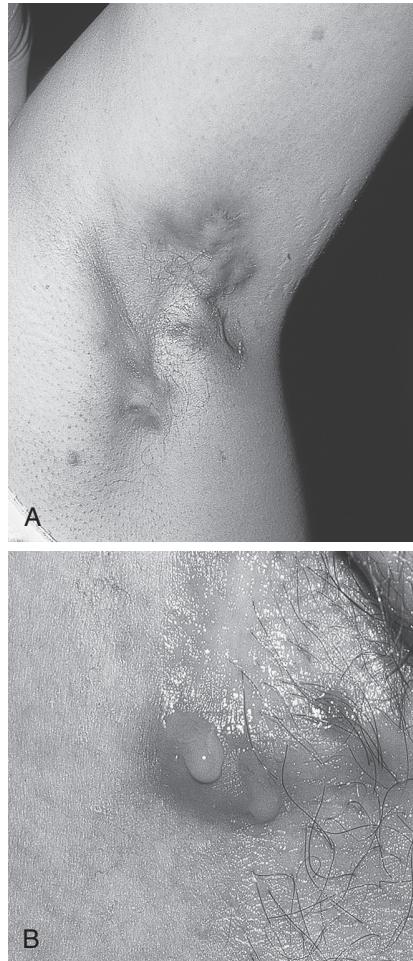
### PHYSICAL FINDINGS & CLINICAL PRESENTATION

The diagnosis is primarily clinical based on the development of typical lesions in a characteristic distribution, with a relapsing nature.

- Early symptoms include pain, itching, burning, erythema, and hyperhidrosis.
- Typical lesions include:
  1. Painful erythematous papules and nodules leading to painful abscesses with foul-smelling discharge.
  2. Dermal contractures and ropelike elevation of the skin.
  3. Comedones in the apocrine, gland-bearing skin.
- Classified into Hurley Stages
  1. Stage I: abscesses without sinus tracts or scarring.
  2. Stage II: multiple abscesses plus sinus tracts and scarring.
  3. Stage III: diffuse involvement of entire area with abscesses, sinus tracts, and scarring.
- The axilla is the most common site (Fig. H1-46).
- Less common sites include the inguinal region, the breasts more often in women, and the perineal or perianal skin more often in men.
- There is a strong tendency toward relapse and recurrence.
- There is often a poor response to conventional antibiotics and no pathogens isolated from cultures of lesions.
- The disease is often mistaken for a simple infection and a long delay in diagnosis is common.

### ETIOLOGY

- Keratinous materials plug apocrine glands in hair follicles leading to stasis, dilation, rupture, and re-epithelialization.
- Bacteria are trapped and multiply leading to gland rupture with surrounding inflammation and local bacterial infection.
- Over time, repeated nodules and infections cause scarring, which can lead to deep tissue damage and sinus tracts.
- Infectious agents such as *Streptococcus*, *Staphylococcus*, and *Escherichia coli*, and enteric flora have been identified in cultures, but are likely a secondary component of the disease.
- There is likely a significant genetic component to the disease. An HS spectrum of different phenotypes has been characterized involving genetic factors that are not yet well described but may be important for future therapy.



**FIGURE H1-46 Hidradenitis suppurativa (HS).** **A**, HS of the axilla. This is the classic appearance with inflammatory nodules and scarred areas. This condition is commonly misdiagnosed as a bacterial infection. **B**, HS of the axilla; a close-up view of the draining pus. When intact, the lesions represent sterile abscesses. Once open, they may become secondarily infected. (From White GM, Cox NH [eds]: *Diseases of the skin: a color atlas and text*, ed 2, St Louis, 2006, Mosby.)

- HS has been associated with other endocrine and autoimmune disorders such as diabetes, Cushing's disease, acromegaly, Crohn's disease, and inflammatory arthritis.
- Metabolic syndrome affects as many as 50% of patients with HS and may exacerbate the associated inflammation.

## Dx DIAGNOSIS

### DIFFERENTIAL DIAGNOSIS

- Follicular pyoderma such as folliculitis, furuncles, carbuncles, and pilonidal cysts.
- Granuloma inguinale.
- Perianal and vulvar manifestations of Crohn's disease.
- Actinomycosis.
- Lymphogranuloma venereum.
- Dermoid, epidermoid, or Bartholin's cysts.
- Tuberculous inflammation of the skin.
- Lymphadenitis.
- Erysipelas.

### WORKUP

Primarily a clinical diagnosis based on typical lesion (see "Physical Findings & Clinical Presentation").

### LABORATORY TESTS

- Patients with acute lesions may have an elevated erythrocyte sedimentation rate or WBC.
- Febrile and toxic appearing patients should have complete blood count, chemistries, and blood cultures.
- Any pus should be sampled for bacterial culture and sensitivity.

## Rx TREATMENT

There is no definitive cure for hidradenitis.

### NONPHARMACOLOGIC THERAPY

- Weight loss and control of metabolic syndrome.
- Smoking cessation.
- Avoidance of shaving, depilatory creams, deodorants.
- Warm compresses.
- Incision and drainage of nonpurulent lesions is *not* recommended due to recurrence and scarring.
- Laser therapy, radiotherapy, and cryotherapy currently under study.
- Wide local excision for stage III disease with or without vacuum-assisted closure device.

### ACUTE AND CHRONIC Rx

- NSAIDs for inflammation and pain, consider gabapentin, pregabalin, SSRIs for chronic pain management.
- Antibiotics never proven to be effective; however, are mainstay of treatment. Can base treatment on the basis of aspirate culture and sensitivities or empirically.
  1. Clindamycin is the only topical antibiotic proven to be effective in randomized controlled trial and is appropriate for stage I disease.

2. For oral therapy in stage II: consider clindamycin and rifampin in combination. Cephalosporins, dicloxacillin, erythromycin, minocycline, and tetracycline have also been used.
  3. Severe, recurrent disease can require up to 3 to 6 mo of antibiotics.
- Oral contraceptives with low androgenic progesterone (norgestimate, desogestrel, or gestodene) for women show mixed effectiveness.
  - Isotretinoin has been used with mixed effectiveness.
  - Metformin has mixed effectiveness, possibly due to related metabolic syndrome and hyperandrogenism.
  - Corticosteroids and other immune suppressants such as cyclosporin, infliximab, and etanercept have been used for stage II disease, with mixed results.
  - Adalimumab, an anti-tumor necrosis factor- $\alpha$  antibody given once per week (dose 40 mg/wk) has been used with mixed results, and further studies are needed.

### COMPLICATIONS

- Squamous cell carcinoma.
- Scarring leading to restricted limb mobility or lymphedema.
- Rectal or urethral fistulas.
- Psychological effects related to disfiguring nature of disease.

### REFERRAL

- Referral to dermatology during stage I to II disease.
- Referral to a surgeon is indicated for stage III disease.

- It is important to maximize nonmedical treatment, start medical treatment, and refer to a surgeon early in the disease course to ensure the best quality of life for patients.
- The only definitive treatment for hidradenitis is wide excision of the involved skin.

### SUGGESTED READINGS

Available at [www.expertconsult.com](http://www.expertconsult.com)

AUTHOR: MARY BETH SUTTER, M.D.

## PEARLS & CONSIDERATIONS

### COMMENTS

- Patients with hidradenitis are at risk for severe depression, social isolation, and negatively impacted sexuality as a result of their disease.
- There is an average delay in diagnosis of 12 years and most patients are diagnosed in stage II of the disease.

## SUGGESTED READINGS

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## BASIC INFORMATION

### DEFINITION

*High-altitude illness* refers to a spectrum of cerebral and pulmonary syndromes related to hypoxemia occurring during rapid ascension to high altitudes. Common acute syndromes include high-altitude pulmonary edema (HAPE), acute mountain sickness (AMS), and high-altitude cerebral edema (HACE). The latter two are thought to represent different points of severity along the same pathophysiologic process in the brain.

### SYNOMYS

Altitude sickness  
High-altitude headache  
Acute mountain sickness  
High-altitude pulmonary edema  
High-altitude cerebral edema

### ICD-9CM CODES

289 Mountain sickness, acute  
993.2 High altitude, effects

### ICD-10CM CODES

W94 Exposure to high and low air pressure and changes in air pressure  
T70.2 Other and unspecified effects of high altitude

### EPIDEMIOLOGY & DEMOGRAPHICS

- More than 30 million people are at risk of developing altitude sickness.
- 80% of people who ascend to high altitudes have HAH<sub>2</sub>.
- AMS is the most common of the altitude diseases. It affects approximately 40% to 50% of people ascending to 14,000 ft (4200 m) from lowland.
- The incidence of HACE is reported to be 0.1% to 2% at elevations in excess of 12,000 ft (3000 m). HACE is often complicated by concomitant HAPE.
- Men are five times more likely to develop HAPE than are women.
- AMS and HACE affect men and women equally.

### PHYSICAL FINDINGS & CLINICAL PRESENTATION (Table EH1-23)

#### HAH<sub>1</sub>

- Headache that develops within 24 hr of ascent.
- Bilateral, frontal or frontotemporal, dull or pressing quality.
- Mild to moderate intensity and aggravated by exertion, movement, straining, coughing, or bending.
- Headache resolves within 8 hr of descent.
- HAH should resolve with analgesics and/or 10 to 15 min of supplementary oxygen.
- Difficult to distinguish from headaches secondary to dehydration.

#### AMS

- AMS is thought to be a progression of HAH<sub>2</sub>.

- Occurs within 6 to 12 hours after rapid ascent to 8000 ft (2500 m) in 10% to 25% of unacclimatized persons.
- Headache is the most common symptom.
- Dizziness and lightheadedness.
- Nausea, vomiting, and loss of appetite.
- Fatigue.
- Sleep disturbance from an exaggerated hyperventilatory phase of Cheyne-Stokes respiration in response to hypoxemia and alkalosis.
- AMS can evolve into HAPE and HACE.
- Retinal hemorrhages can be present from increased blood flow or breakdown in the blood-retina barrier.
- Supplemental oxygen may be used to support the clinical diagnosis.

#### HAPE (Fig. EH1-47A)

- Typically occurs 2 to 4 days after ascent over 8000 ft (2500 m).
- Dyspnea, loss of stamina.
- Dry cough or cough with frothy rust- or pink-tinted sputum.
- Chest tightness.
- Tachycardia, tachypnea, rales, cyanosis.

#### HACE

- Usually presents several days after AMS.
- Confusion, irritability, drowsiness, stupor, hallucinations, mild fever.
- Headache, nausea, vomiting.
- Truncal ataxia, paralysis, and seizures.
- The sixth cranial nerve is the most commonly affected from the compression of the trunk adjacent to brain swelling.
- Coma and death from brain herniation may develop within hours of the first symptoms.

### ETIOLOGY

- During ascent to altitudes above sea level, the atmospheric pressure decreases. Although the percentage of oxygen in the air remains the same, the partial pressure of oxygen decreases with increased altitude, and can cause hypoxemia. Fig. EH1-47B illustrates the effect of altitude on alveolar Pao<sub>2</sub> and oxygen saturation.
- Increased cerebral blood flow and the loss of autoregulation of intracranial pressure may contribute to increased cerebral vascular permeability and subsequent brain edema.
- Hypobaric hypoxia can trigger elevated pulmonary pressures, resulting in protein-rich, hemorrhagic exudates into the lung alveoli

due to a breakdown in the pulmonary blood-gas barrier (HAPE).

- The body responds to low oxygen partial pressures through a process of acclimatization (see "Comments").

## Dx DIAGNOSIS

Made by clinical presentation and physical findings.

### DIFFERENTIAL DIAGNOSIS

- Dehydration.
- Carbon monoxide poisoning.
- Hypothermia.
- Infection.
- Substance abuse.
- Congestive heart failure.
- Pulmonary embolism.
- Cerebrovascular accident.
- Box H1-5 summarizes the differential diagnosis of high-altitude illnesses.

### WORKUP

Typically the diagnosis is self-evident after history and physical examination. Laboratory tests and imaging studies help monitor cardiopulmonary and central nervous system status in patients admitted to the intensive care unit for pulmonary and/or cerebral edema. In patients with HAPE occurring at lower altitudes (<8000 ft), an evaluation of preexisting pulmonary hypertension or a left-to-right shunt should be considered.

### LABORATORY TESTS

Not useful, unless to rule out an alternative diagnosis.

### IMAGING STUDIES

- Chest x-ray showing Kerley B-lines and patchy edema (see Fig. EH1-47A).
- CT scan of the head showing diffuse or patchy edema.
- MRI of the head showing characteristic intense T2 signal in the white matter.

## Rx TREATMENT

#### Nonpharmacologic Therapy

- Stop the ascent to allow acclimatization or start to descend until symptoms have

### BOX H1-5 Differential Diagnosis of High-Altitude Illnesses

#### Acute mountain sickness and high-altitude cerebral edema

Dehydration, exhaustion, viral or bacterial infection, alcohol hangover, hypothermia, carbon monoxide poisoning, migraine, hyponatremia, hypoglycemia, diabetic ketoacidosis, CNS infection, transient ischemic attack, arteriovenous malformation, stroke, seizures, brain tumors, ingestion of toxins or drugs, acute psychosis

#### High-altitude pulmonary edema

Asthma, bronchitis, pneumonia, mucus plugging (secondary to previous), hyperventilation syndrome, pulmonary embolus, heart failure, myocardial infarction

CNS, Central nervous system.

From Auerbach P: *Wilderness medicine, expert consult Premium Edition—Enhanced Online Features and Print*, Philadelphia, 2012, Saunders.

resolved. Descent is the definitive treatment and should begin immediately at the first suspicion of HACE.

- Oxygen 4 to 6 L/min is used for severe AMS, HAPE, and HACE.
- Portable hyperbaric bags are useful if available at the site.
- Altitude can cause diuresis that may be mediated by enhanced release of atrial natriuretic peptide. When coupled with the increased fluid loss through increased ventilation, there is a higher risk for dehydration, and adequate hydration should be maintained.

#### ACUTE PHARMACOLOGIC Rx

- Nonsteroidal anti-inflammatory drugs (e.g., ibuprofen 600 mg every 6 hours, beginning 6 hours before ascending) are effective prophylaxis of traditional altitude sickness and in treating headaches in AMS.
- Acetazolamide 125 to 250 mg PO bid has been effective for both prevention and acute therapy in patients with AMS and HACE.
- Nifedipine 10 mg sublingual followed by long-acting nifedipine 30 mg bid is used for patients with HAPE who cannot descend immediately.
- Dexamethasone 4 mg PO every 6 hr is used in patients with severe AMS, HAPE, or HACE.

#### CHRONIC Rx

Prevention is the most prudent therapy.

- Slow, staged ascent to avoid altitude sickness.
- Start the ascent below 8000 feet.
- Ascend 1000 feet/day (300 m/day).

#### BOX H1-6 Field Treatment of High-Altitude Illness

##### High-Altitude Headache and Mild Acute Mountain Sickness

- Stop ascent, rest, acclimatize at same altitude.
- Symptomatic treatment as necessary with analgesics and antiemetics.
- Consider acetazolamide, 125 to 250 mg bid, to speed acclimatization.
- OR descend 500 m (1640 feet) or more.

##### Moderate to Severe Acute Mountain Sickness

- Low-flow oxygen, if available.
- Acetazolamide, 125 to 250 mg bid, with or without dexamethasone, 4 mg PO, IM, or IV q6h.
- Hyperbaric therapy.
- OR immediate descent.

##### High-Altitude Cerebral Edema

- Immediate descent or evacuation.
- Oxygen, 2 to 4 L/min.
- Dexamethasone, 8 mg PO, IM, or IV, then 4 mg q6h.
- Hyperbaric therapy.

##### High-Altitude Pulmonary Edema

- Minimize exertion and keep warm.
  - Immediate descent or hyperbaric therapy.
  - Oxygen, 4 to 6 L/min until improving, then 2 to 4 L/min.
- If above unavailable, one of the following:
- Nifedipine, 30 mg extended release q12h.
  - Sildenafil 50 mg q8h.
  - Tadalafil 10 mg q12h.
  - Consider inhaled  $\beta$ -agonist.

##### Periodic Breathing

- Acetazolamide, 62.5 to 125 mg at bedtime as needed.

4. Spend two nights at the same altitude every 3 days.

5. Sleep at lower heights than the altitude climbed ("climb high, sleep low").

6. Prophylactic therapy with NSAIDs (ibuprofen 600 mg every 6 hours, beginning 6 hours before ascending) or acetazolamide up to 750 mg daily and/or dexamethasone 8 to 16 mg daily decreases the risk of developing AMS (combination may have additive benefit). The drugs should be used until acclimatization occurs.

7. Prophylactic inhalation of a  $\beta$ -adrenergic agonist, salmeterol 125 mcg q12h, or the use of slow-release nifedipine 20 mg bid have both been shown to reduce the risk of HAPE in susceptible individuals.

8. Tadalafil, a long-acting phosphodiesterase inhibitor, has recently been shown to decrease the incidence of HAPE in susceptible individuals.

9. Box H1-6 summarizes field treatment of high-altitude illness.

#### DISPOSITION

- AMS improves over a period of 2 to 3 days.
- HAPE is the most common cause of death among patients with altitude illnesses.
- More than 60% of patients with HAPE will have recurrence of symptoms on subsequent climbs.
- In HACE, neurologic deficits may persist for weeks but eventually resolve. If coma occurs, prognosis is poor.

#### REFERRAL

Cardiology and neurology referrals are made in patients with pulmonary edema and central nervous system findings, respectively.



#### PEARLS & CONSIDERATIONS

##### COMMENTS

- Acclimatization is the process in which an individual who normally resides at low altitude adapts to hypobaric hypoxia to improve tolerance and performance at higher altitude. These mechanisms include:
  - An increase in respiratory rates and tidal volume. This hyperventilation allows lowering of arterial carbon dioxide to preserve oxygen delivery, even at extreme altitudes.
  - An early increase in heart rate and stroke volume to improve oxygen delivery. After 1 wk, both parameters decrease because of diuresis and lower catecholamine levels.
  - Pulmonary hypertension develops in response to hypoxemia, resulting in improvement of the ventilation-perfusion mismatch but may be maladaptive and lead to the development of HAPE.
  - Cerebral vasodilation to increase blood flow to the brain.
  - Rise in hemoglobin and hematocrit. This is a long-term process that takes up to 1 wk to occur in response to the need for improved oxygen delivery.
- Adaptation to altitude is different from acclimatization and refers to physiologic differences in permanent residents at high altitude (e.g., an increased oxygen diffusion capacity).
- High altitude illness can generally be prevented by ascending to 300 to 500 meters per day at altitudes above 3000 meters and including a rest day every 3 to 4 days.
- Risk factors for the development of altitude sicknesses are:
  - Rapid ascent.
  - Previous history of altitude sickness.
  - Strenuous exertion on arrival.
  - Obesity.
  - Male gender.
- Physical fitness is not protective against high-altitude illness.
- Both dexamethasone and tadalafil decrease systolic pulmonary artery pressure and may reduce the incidence of HAPE in adults with a history of HAPE. Dexamethasone prophylaxis may also reduce the incidence of AMS in these adults.
- Descent is mandatory for all persons with HACE or HAPE.

#### SUGGESTED READINGS

Available at [www.expertconsult.com](http://www.expertconsult.com)

#### RELATED CONTENT

Altitude Sickness (Patient Information)

AUTHORS: JOHANNES STEINER, M.D., and RICHARD REGNANTE, M.D.

## SUGGESTED READINGS

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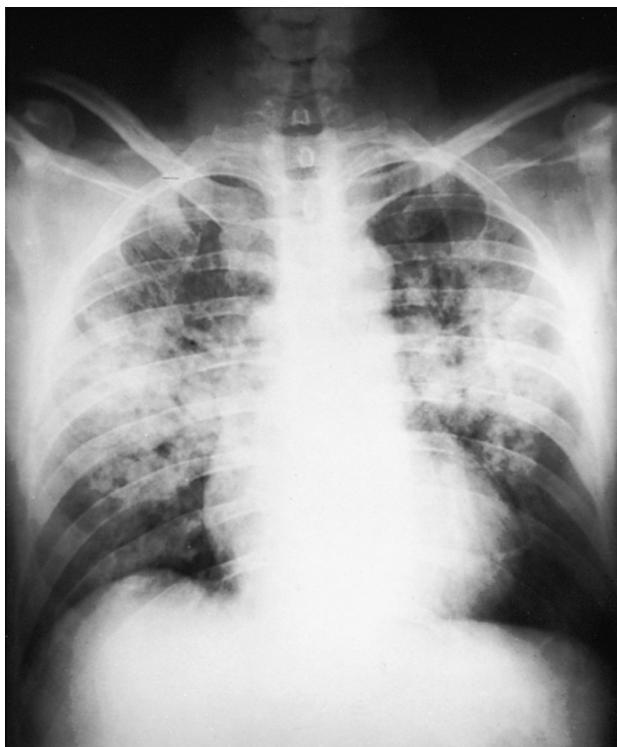
**TABLE EH1-23** Clinical Characteristics of High-Altitude Illnesses

	Clinical Classification			
	HAH	Mild AMS	Moderate to Severe AMS	HACE
Symptoms	Headache only	Headache plus one more symptom (nausea/vomiting, fatigue/lassitude, dizziness or difficulty sleeping) All symptoms of mild severity	Headache plus one or more symptoms (nausea/vomiting, fatigue/lassitude, dizziness or difficulty sleeping) Symptoms of moderate to severe intensity	±Headache Worsening of symptoms seen in moderate to severe AMS
LL-AMS score*	1-3, headache only	2-4	5-15	
Physical signs	None	None	None	Ataxia Altered mental status
Findings	None	None	Antidiuresis Slightly increased body temperature Slight desaturation Widened A-a gradient Elevated ICP White matter edema (CT, MRI)	HAPE common: positive chest radiograph, rales, dyspnea at rest Elevated ICP White matter edema (CT, MRI)
Pathophysiology	Unknown; cerebral vasodilation, trigeminal vascular system?	Unknown; same as HAH?	Vasogenic edema; cytotoxic edema?	Advanced vasogenic cerebral edema; cytotoxic edema?

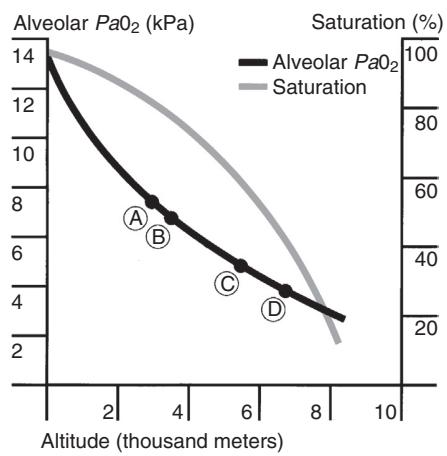
AMS, Acute mountain sickness; CT, computed tomography; HACE, high-altitude cerebral edema; HAH, high-altitude headache; HAPE, high-altitude pulmonary edema; ICP, intracranial pressure; MRI, magnetic resonance imaging.

\*The self-reported Lake Louise AMS score.

From Auerbach P: *Wilderness medicine, expert consult Premium Edition—Enhanced Online Features and Print*, Philadelphia, 2012, Saunders, Elsevier. 978-1-4377-1678-8.



**FIGURE EH1-47 A** Chest radiograph showing high-altitude pulmonary edema. (From Strauss RH [ed]: *Sports medicine*, ed 2, Philadelphia, 1991, Saunders.)



**FIGURE EH1-47 B** Effect of altitude on alveolar  $\text{PaO}_2$  and oxygen saturation. Because of the steep slope of the oxygen dissociation curve, increasing altitude above 5000 m causes abdominal cramps and nausea; **B**, 3500 m (12,000 ft)—headache, nausea, diminished visual acuity, and possible precipitous fall in saturation. In an unacclimated person, acute change occurs at **(B)** 3000 m (10,000 ft)—slightly impaired memory and judgment, increased heart rate pulmonary edema; **C**, 5500 m (18,000 ft)—impaired consciousness after several hours in many people; and **D**, 6750 m (22,000 ft)—loss of consciousness. (From Souhami RL, Moxham J: *Textbook of medicine*, ed 4, London, 2002, Churchill Livingstone.)



## BASIC INFORMATION

### DEFINITION

Hip fractures are classified as intracapsular or extracapsular. Intracapsular fractures include femoral head and femoral neck fractures (Fig. H1-48). These fractures are further categorized as either displaced or nondisplaced. Extracapsular fractures include intertrochanteric and subtrochanteric fractures, as well as the less common greater and lesser trochanteric fractures. These fractures can be further categorized by the degree of comminution.

### SYNOMS

Hip fracture  
Intracapsular fracture  
Subcapital fracture  
Extracapsular fracture  
Intertrochanteric fracture

#### ICD-9CM CODES

- 820.8 Femoral neck fracture
- 820.2 Peritrochanteric fracture

#### ICD-10CM CODES

- S72.0 Fracture of neck of femur
- S72.1 Peritrochanteric fracture
- S72.2 Subtrochanteric fracture
- S72.3 Fracture of shaft of femur
- S72.4 Fracture of lower end of femur
- S72.7 Multiple fractures of femur
- S72.8 Fractures of other parts of femur
- S72.009A Fracture of unspecified part of neck of unspecified femur, initial encounter for closed fracture

### EPIDEMIOLOGY & DEMOGRAPHICS

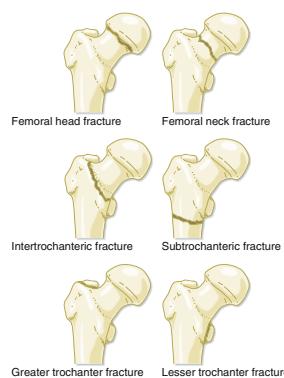
**PREVALENCE:** Lifetime risk in women ~16%.

**PREDOMINANT SEX:** Female/male ratio of 3:1.

**PREDOMINANT AGE:** 90% >60 yr.

### PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Hip or groin pain.
- Affected limb usually shortened and externally rotated in displaced fractures.



**FIGURE H1-48** Types of hip fractures. (From Adams JG.; et al. *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.)

- Impacted fractures: possibly no deformity and only mild pain with hip motion.
- Mild external bruising.

### RISK FACTORS

- Osteoporosis.
- Age >75.
- Gait instability, foot deformities, muscular weakness.
- Sensory impairment.
- Polypharmacy.
- Impaired cognition, depression.
- Use of alcohol or benzodiazepines.
- Orthostatic hypotension.
- Environmental hazards at home (e.g., loose rugs, loose cords).
- Subclinical hyperthyroidism.

### ETIOLOGY

- Trauma.
- Age-related bone weakness, usually caused by osteoporosis.
- Increased risk of fractures in elderly (decline in muscle function, use of psychotropic medication, etc.).

## Dx DIAGNOSIS

### DIFFERENTIAL DIAGNOSIS

- OA of hip, RA of hip.
- Hip dislocation.
- Pathologic fracture.
- Lumbar disk syndrome with radicular pain.
- Insufficiency fracture of pelvis.
- Trochanteric bursitis.
- Septic hip joint.
- Pelvic fracture.
- Lateral femoral cutaneous nerve entrapment (meralgia paresthetica).
- Osteitis deformans (Paget's disease).

### WORKUP

Diagnosis is usually obvious based on clinical and radiographic findings (Figs. H1-49 and H1-50). Fig. H1-51 illustrates the Garden classification of femoral neck fractures.

### IMAGING STUDIES

- Standard roentgenograms consisting of an anteroposterior view of the pelvis and a cross-table lateral view of the hip to confirm the diagnosis.
- If initial roentgenograms are negative and diagnosis of an occult femoral neck fracture is suspected, hospital admission and further radiographic assessment with either bone scanning or MRI are recommended.
- Bone scanning is sensitive after 48 to 72 hr.

## Rx TREATMENT

- Orthopedic consultation.
- Surgery indicated in most cases, usually within 24 hr. Treatment depends on type of fracture:
  1. Femoral neck, non-displaced, impacted valgus: cannulated screws.

2. Displaced: <50 yr, emergent reduction, cannulated screws; >50 yr: hemiarthroplasty, unipolar versus bipolar or total hip arthroplasty if preexisting degenerative changes
3. Intertrochanteric: stable, 2 and 3 parts, dynamic hip screw (DHS) versus trochanteric femoral nail (TFN); unstable, 4 parts, subtrochanteric extension, TFN.
4. Reverse obliquity: TFN, blade plate, dynamic condylar screw, not DHS.
- Deep vein thrombosis prophylaxis (fondaparinux, LMWH, vitamin K antagonist). Mechanical prophylaxis is contraindicated. Prophylaxis is usually continued for 28 to 35 days postop.
- Pain management: effective pain management is a primary goal in hip fracture. Opioid analgesics have a high incidence of delirium and constipation. Nerve blockade is effective in reducing acute pain after hip fracture.
- Prophylactic antibiotics should be initiated before surgery and continued for 24 hours after surgical repair.
- Rehabilitation is a major component of hip fracture treatment and should be initiated on the first postoperative day.
- Conservative therapy in patients who are not surgical candidates (too ill for surgery, bed- or wheelchair-bound patients before injury).

### DISPOSITION

- Surgical mortality after hip fracture repair is 2% to 3%. Older adults have a 5- to 8-fold increased risk for all-cause mortality during the first 3 mo after hip fracture. Mortality rate within 1 yr in elderly patients is 25% to 30%. Excess annual mortality persists over time for both women and men, but at any given age, excess annual mortality after hip fracture is higher in men than in women.
- Dementia is a particularly poor prognostic sign.

### REFERRAL

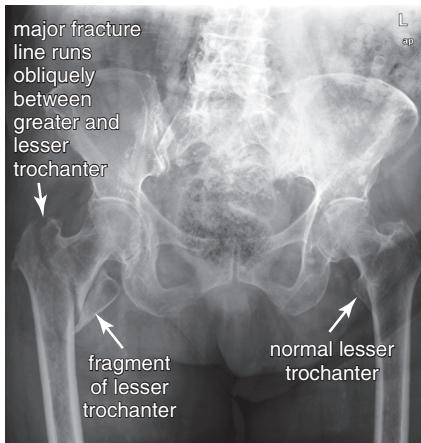
For surgical consideration when the diagnosis is made.



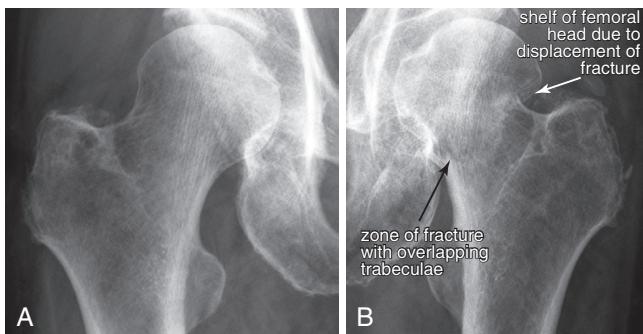
## PEARLS & CONSIDERATIONS

### COMMENTS

- Complications: nonunion, avascular necrosis, DVT, infection, delirium, decubitus ulcers, incontinence, persistent pain, loosening of prosthesis.
- Intracapsular fractures: occasionally occur in nonambulatory patients.
  1. Usually treated nonsurgically, especially in the patient with dementia and limited pain perception.
  2. Early bed-to-chair mobilization and vigilant nursing care to avoid skin breakdown.
  3. Fracture usually pain free in a short time even if solid bony healing does not occur.
- As a result of the increasing life span of the female population, femoral neck fractures are becoming more common. The initial



**FIGURE H1-49 Intertrochanteric femur fracture: three parts (proximal, distal, and one trochanter).** Intertrochanteric femur fractures are common, with the mechanism often being a fall from standing in an elderly patient. The major fracture line usually runs obliquely between the greater and the lesser trochanters. These fractures may have two, three, or four parts classically, although badly comminuted combinations are also possible. Two-part fractures consist of the proximal and distal fragments. Three-part fractures also include a fragment of one trochanter. Four-part fractures include fragments of both trochanters. This 86-year-old female had an unwitnessed fall. She has a typical 3-part fracture, with a fragment of the lesser trochanter visible. Note her generalized severe osteopenia. (From Broder JS: *Diagnostic imaging for the emergency physician*, Philadelphia, 2011, Saunders.)

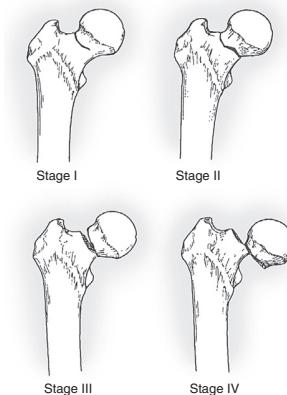


**FIGURE H1-50 Femoral neck fracture.** This 84-year-old female had an unwitnessed fall. **A**, Normal right hip, osteoporotic. **B**, Left hip, another relatively subtle femoral neck fracture. Note the smudging of the trabeculae of the femoral neck. In addition, the distal fragment has shifted medially, creating an overhanging ledge of the femoral head not seen on the opposite normal side. Some femoral neck fractures are more obvious. (From Broder JS: *Diagnostic imaging for the emergency physician*, Philadelphia, 2011, Saunders.)

physical examination and roentgenographic studies may be completely negative. Groin pain, sometimes quite severe, may be the only early clue to the diagnosis.

- The rate of hip fracture could be reduced by:
  1. Elimination of environmental hazards (poor lighting, loose rugs).

2. Regular exercise for balance and strength.
  3. Patient education about fall prevention.
  4. Medication review to minimize side effects.
  5. Prevention and treatment of osteoporosis.
- In the United States, hip fracture rates and subsequent mortality among persons aged 65 yr and older are declining, and comorbidities



**FIGURE H1-51 Garden classification of femoral neck fractures.** (From Kyle RF; *Fractures of the hip*. In Gustilo RB et al [eds]: *Fractures and dislocations*, St Louis, 1993, Mosby.)

among patients with hip fractures are very expensive (\$40,000 in the first year following hip fracture for direct medical costs and \$5000 in subsequent years).

- Fragility (or low-trauma) hip fractures, common in elderly patients with reduced bone density, carry a 1-yr mortality of 26%, while another 58% require long-term care in a nursing facility. Previous fragility hip fracture is associated with a second osteoporotic fracture within the subsequent 5 yr.
- Concurrent prolonged use of proton-pump inhibitors ( $\geq 1$  yr) is associated with reduced effectiveness of alendronate for preventing hip fractures in older adults.

## EBM EVIDENCE

Available at [www.expertconsult.com](http://www.expertconsult.com)

## SUGGESTED READINGS

Available at [www.expertconsult.com](http://www.expertconsult.com)

## RELATED CONTENT

Hip Fracture (Patient Information)

AUTHOR: FRED F. FERRI, M.D.



## EVIDENCE

### Abstract<sup>[1]</sup>

We performed a 4-year follow-up of a randomized controlled trial involving 120 elderly patients with an acute displaced femoral neck fracture who were randomized to treatment with either a bipolar hemiarthroplasty or a total hip arthroplasty. The difference in hip function (as indicated by the Harris hip score) in favor of the total hip arthroplasty group that was previously reported at one year persisted and seemed to increase with time (mean score, 87 compared with 78 at 24 months [ $p < 0.001$ ] and 89 compared with 75 at 48 months [ $p < 0.001$ ]). The health-related quality of life (as indicated by the EuroQol [EQ-5D<sub>index</sub>] score) was better in the total hip arthroplasty group at the time of each follow-up, but the difference was significant only at 48 months ( $p < 0.039$ ). These results confirm the better results in terms of hip function and quality of life after total hip arthroplasty as compared with hemiarthroplasty in elderly, lucid patients with a displaced fracture of the femoral neck. **A**

### Abstract<sup>[2]</sup>

**Background:** Both intramedullary nails and sliding hip screws are used with good results in the treatment of intertrochanteric and subtrochanteric fractures. The aim of our study was to assess whether use of the TRIGEN INTERTAN nail, as compared with a sliding hip screw, resulted in less postoperative pain, improved functional mobility, and reduced surgical complication rates for patients with an intertrochanteric or subtrochanteric fracture.

**Methods:** In a prospective, randomized multicenter study, 684 elderly patients were treated with the INTERTAN nail or with a sliding hip screw with or without a trochanteric stabilizing plate. The patients were assessed during their hospital stay and at 3 and 12 months postoperatively. A visual analogue scale (VAS) pain score was recorded at all time points, and functional mobility was assessed with use of the timed Up & Go test. The Harris hip score (HHS) was used to assess hip function more specifically. Quality of life was measured with the EuroQol-5D (EQ-5D). Radiographic findings as well as intraoperative and postoperative complications were recorded and analyzed.

**Results:** Patients treated with an INTERTAN nail had slightly less pain at the time of early postoperative mobilization (VAS score, 48 versus 52;  $p = 0.042$ ), although this did not influence the length of the hospital stay and there was no difference at three or twelve months. Regardless of the fracture and implant type, functional mobility, hip function, patient satisfaction, and quality-of-life assessments were comparable between the groups at 3 and 12 months. The numbers of patients with surgical complications were similar for the 2 groups (29 in the sliding-hip-screw group and 32 in the INTERTAN group,  $p = 0.67$ ).

**Conclusions:** INTERTAN nails and sliding hip screws are similar in terms of pain, function, and reoperation rates twelve months after treatment of intertrochanteric and subtrochanteric fractures. **A**

### Abstract<sup>[3]</sup>

Hip Fracture

#### Objective:

Head-preserving fracture care especially for the elderly may be complicated by acetabular screw penetration, cut out, delayed union or femoral head necrosis. The following comparative study analyses whether a new angular stable device may overcome these shortcomings.

#### Material and Methods:

The Targon FN plate (B.Braun/Aesculap, Germany) employs up to 4 angular stable telescoping screws for the fixation of the head fragment. In a prospective study patients with displaced and undisplaced intracapsular femoral neck fractures were treated by closed reduction and fracture fixation using either the Targon FN implant or a standard sliding hip screw (SHS). Patients were followed up clinically, radiographically and via telephone at a mean of follow-up time of 15.5 months.

#### Results:

A group of 52 patients (mean age: 67 years) with femoral neck fractures were treated with either Targon FN (27 patients) or SHS (25 patients). Time for surgery did not differ within the two groups (56 min Targon FN versus 55 min SHS). 8 patients with SHS (32%) and 4 patients (15%)

with Targon FN experienced cut out of the lag screw and received hip replacement ( $p < 0.05$ ). Implant failure occurred after a mean of 1.8 months after SHS and 6.0 months after Targon FN implantation. Final radiographs revealed substantial subsidence in both groups (5.0 mm Targon FN; 9.8 mm SHS,  $p \approx 0.055$ ) with a clear trend to less subsidence for the Targon FN group. Furthermore, asymmetrical telescoping of the lag screws occurred in 30% (n=8), complete depletion of telescoping distance in 11% (n=3) in the Targon FN group. Functional assessment using the HHS assessment tool, however, presented with slightly better results for the SHS treatment ( $87.7 \pm 13.9$ ) when compared with Targon FN fixation ( $69.5 \pm 4.5$ ).

#### Conclusions:

The study revealed less subsidence of the head fragment, lower cut out rate and a lower rate of conversion to hemiarthroplasty after Targon FN fixation in comparison with a standard SHS fixation in a small number of patients with hip fractures. However, this was not accompanied by functional limitations in the SHS group. **B**

### Abstract<sup>[4]</sup>

#### Introduction:

Immediate total hip replacement (THR) in patients with acetabular fractures is controversial because of concerns about high complication rates. The current article is a systematic review of the literature on the use of acute THR for the treatment of acetabular fractures.

#### Materials and Methods:

This systematic review included studies published in English between 1992 and 2012 of subjects with acetabular fracture undergoing immediate THR. Outcomes of interest included indications; clinical assessment, including walking ability; comparison with control group; associated procedures, and rate of complications, such as loosening or revision surgery.

#### Results:

This review identified 6 studies, of which only one included a control group. Acute THR was associated with satisfying outcomes with regard to clinical assessment and walking ability. The comparative study assessed the difference between acute THR and delayed THR in acetabular fractures: improved outcomes were observed in the delayed THR group, although the differences between the two groups were not statistically significant.

#### Discussion:

According to data reported in the literature, acute primary THR can be successful in patients with poor bone quality, combined acetabular and femoral neck fractures, or pathological fractures and concurrent osteoarthritis of the hip. Relative indications include old age, delayed presentation, substantial medical comorbidities, and pathologic obesity. Clinical outcomes with acute THR were similar to those with delayed THR. Although the results reported in the six studies reviewed here were satisfying overall, there is limited evidence in this area in the existing literature and future prospective investigations are required.

#### Conclusion:

Data reported in the literature indicate that immediate THR can be successful in appropriately selected elderly patients or patients with extensive osteoporosis, combined acetabular and femoral neck fractures or pathological fractures. There is currently a limited evidence base for THR in patients with acetabular fractures; therefore, physicians' practice and expertise are the most useful tools in clinical practice. **B**

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## BASIC INFORMATION

### DEFINITION

Hirsutism is the development of stiff, pigmented (terminal) facial and body hair (male distribution) in women as a result of excess androgen production.

### SYNOMS

Excessive hair growth

#### ICD-9CM CODES

704.1 Hirsutism

#### ICD-10CM CODES

L68.0 Hirsutism

### EPIDEMIOLOGY & DEMOGRAPHICS

- Overall prevalence unknown, estimated 5% to 10% in reproductive age women.
- Race and genetics should be considered. Some distinct ethnic populations have minimal body hair and others (Mediterranean, Middle Eastern, South Asian) have moderate to large amounts of body hair while serum androgen levels are similar.
- Social norms and culture also determine how much body hair is cosmetically acceptable.
- Half of all cases of mild hirsutism do not have hyperandrogenemia. "Patient-important hirsutism" refers to hirsutism causing woman sufficient distress to seek care.
- Incidence and presentation of hirsutism is dependent on underlying cause of androgen excess (see "Differential Diagnosis").
- Most women with hirsutism have polycystic ovary syndrome.

### PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Timing of symptoms: abrupt onset, short duration, rapid progression, progressive worsening, more severe signs of virilization, or later age of onset suggest androgen-pro-

ducing tumor, late-onset congenital adrenal hyperplasia, or Cushing's syndrome. Weight increases may produce increased androgen production.

- Menstrual history: menarche, cycle regularity and symptoms of ovulation, fertility, and contraception use. Anovulatory cycles are the most common underlying cause of androgen excess.
- Medication use history: some drugs cause hirsutism or produce androgenic effects (danazol, phenytoin, valproic acid, androgenic progestins (e.g., norgestrel), cyclosporin, minoxidil, metoclopramide, phenothiazines, methyldopa, diazoxide, penicillamine).
- Family history: known or suspected family history of hirsutism, congenital adrenal hyperplasia, insulin resistance, polycystic ovary syndrome (PCOS), infertility, obesity, menstrual irregularity may be found.
- Physical exam reveals deepening voice, body habitus, increased muscle mass, galactorrhea; abdominal and pelvic exam.
- Associated cutaneous manifestations (Fig. H1-52) are acne, acanthosis nigricans, striae, hair distribution, location and quantity, frontotemporal balding, muscle mass, clitoromegaly.
- Ferriman-Gallwey scale, a simple, pictorial system of scoring nine body areas, is the most common tool used to quantify hirsutism. It may be unreliable in non-Caucasian women of other ethnicities.

### ETIOLOGY

- Presence of hirsutism indicates androgen excess. Total testosterone may be normal, but free testosterone is elevated.
- Androgens induce vellus hair follicles (soft, unpigmented hair) in sex-specific areas (upper lip, chin, midsternum, upper abdomen, back, buttocks) to develop into thicker, more heavily pigmented terminal hairs.
- Anovulatory ovaries are usual source of excess androgens through thecal cell steroidogenesis and conversion of androstenedione to testos-

terone. The most common cause of hirsutism is polycystic ovary syndrome, which accounts for three out of every four cases.

- Conditions that decrease hepatic production of sex hormone binding globulin (SHBG) decrease protein-bound testosterone and increase free testosterone fraction (e.g., low estrogen, high androgen, and hyperinsulinemic states).
- Late-onset, congenital adrenal hyperplasia enzyme deficiency (most commonly 21-hydroxylase deficiency) produces excess 17 hydroxyprogesterone (17-OHP) and over-production of androstenedione.
- Rare ovarian tumors primarily derived from Sertoli-Leydig cells, granulosa theca cells, or hilus cells produce excess androgens.
- Rare adrenal tumors produce excess androgens.
- Rare pituitary or hypothalamic tumors produce excess prolactin and can lead to anovulation.
- Box H1-7** summarizes causes of androgen excess in women of reproductive age.

## DX DIAGNOSIS

### DIFFERENTIAL DIAGNOSIS

- Androgen-independent vellus hair: soft, unpigmented hair that covers entire body
- Hypertrichosis: diffusely increased total body hair (vellus or lanugo-type) not restricted to androgen-dependent areas often an adverse response to a medication or systemic illness (e.g., anorexia nervosa, porphyria, malnutrition, hypothyroidism)
- PCOS 75%
- Idiopathic 5% to 15%
- Congenital adrenal hyperplasia 1% to 8%
- Insulin resistance syndrome 3% to 4%
- Cushing's syndrome <1%
- Drug induced <1%
- Ovarian tumor <1%
- Adrenal tumor <1%
- Hyperthecosis <1%
- Hyperprolactinemia <1%

### WORKUP

- Hirsutism is a clinical diagnosis.
- Management of hirsutism is largely independent of the etiology.
- Workup in selected hirsute women is directed to determine underlying cause of androgen excess.
- See specific conditions for more detailed workup of individual diagnoses.

### LABORATORY TESTS

Establishing laboratory evidence of excess androgens in women with moderate or severe hirsutism, sudden onset, rapid progression, or associated menstrual dysfunction, central obesity, clitoromegaly, or acanthosis nigricans is an approach consistent with guidelines from the Endocrine Society, the American College of Obstetricians and Gynecologists, the Androgen Excess and Polycystic Ovary Syndrome Society and the American Association of Clinical Endocrinologists.



**FIGURE H1-52** A patient with an arrenoblastoma with associated polycystic ovaries before and after treatment. **A**, Before treatment, the patient had marked facial hirsutism. **B**, The patient is shown successfully treated. The tumor was resected and ovulation ensued with clomiphene and human chorionic gonadotropin therapy. (From Besser CM, Thorner MO: *Comprehensive clinical endocrinology*, ed 3, St Louis, 2002, Mosby.)

**BOX H1-7 Causes of Androgen Excess in Women of Reproductive Age****Ovarian**

Polycystic ovary syndrome (PCOS)  
Hyperthecosis (a severe PCOS variant)  
Ovarian tumor (e.g., Sertoli-Leydig cell tumor)

**Adrenal**

Nonclassic adrenal hyperplasia  
Cushing's syndrome  
Glucocorticoid resistance  
Adrenal tumor (e.g., adenoma, carcinoma)

**Specific Conditions of Pregnancy**

Luteoma of pregnancy  
Hyperreactio luteinalis  
Aromatase deficiency in fetus

**Other**

Hyperprolactinemia, hypothyroidism  
Medications (danazol, testosterone, anabolizing agents)  
Idiopathic hirsutism (normal serum testosterone in an ovulatory woman)  
Idiopathic hyperandrogenism (patients who do not fall into any of the other categories listed)

From Melmed S et al: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, Saunders.)

- Total plasma testosterone (normal range 20-60 ng/dl [0.69-2.1 nmol/L]) or free testosterone: early morning on day 4 to 10 of menstrual cycle to screen for testosterone-secreting tumors. If moderately or markedly elevated (total testosterone >150 ng/dl [5.2 nmol/L], free testosterone >2 ng/dl [0.07 nmol/L]) may image adrenals and ovaries for androgen-secreting tumors.

Other laboratory test considerations if appropriate:

- Prolactin: moderately elevated values should prompt imaging of pituitary-hypothalamic region
- 17-OHP ( $\alpha$ -hydroxyprogesterone): screen for adrenal enzyme deficiencies. Morning value >200 ng/dl in early follicular phase suggests nonclassic (late onset) congenital adrenal hyperplasia due to 21-hydroxylase deficiency and may be confirmed with high-dose (250 mcg) ACTH stimulation test.
- Thyroid-stimulating hormone (TSH): rule out hypothyroidism
- Dehydroepiandrosterone sulfate (DHEA-S): screen for adrenal androgen production as almost entirely produced by adrenals. Levels >700 mcg/dl (13.6 nmol/L) raise suspicion for adrenal androgen-secreting tumor.

Additional laboratory test considerations if appropriate:

- Follicle-stimulating hormone (FSH): rule out hypoestrogen state (perimenopausal).
- Luteinizing hormone (LH): typically elevated in PCOS with low or normal FSH.
- 24-hour urinary free cortisol: rule out Cushing's syndrome and overproduction of cortisol.
- Overnight single-dose dexamethasone suppression test: rule out Cushing's syndrome and adrenal hyperfunction.
- Fasting blood sugar (FBS), 2-hr 75-g oral glucose tolerance test, fasting insulin levels: rule out insulin resistance syndrome.

**IMAGING STUDIES**

Imaging study considerations if appropriate:

- Pelvic ultrasound (high resolution, transvaginal): rule out ovarian tumor if total testosterone is elevated.
- Abdominal CT/MRI: rule out adrenal tumor if elevated DHEA-S.
- Pituitary-hypothalamic region CT/MRI: rule out pituitary tumor if prolactin elevated.
- Laparoscopy/laparotomy: rule out small ovarian tumor in cases of elevated testosterone levels without radiologic evidence of adrenal or ovarian pathology.

**RX TREATMENT****NONPHARMACOLOGIC THERAPY**

- Weight reduction: can reduce androgen production indirectly by reducing insulin-stimulated theca cell androgen production and improve menstrual function, and slow hair growth in obese women.
- Cosmetic: temporary.
  - Shaving: does not stimulate hair growth; lasts days, leaves stubble.
  - Epilation: electronic plucking.
  - Bleaching: removes hair pigment. May cause skin irritation.
  - Mechanical waxing/plucking.
  - Depilatories: gels, lotions, or creams that chemically disrupt sulfide bonds of hair causing dissolution of hair shaft. No stubble.
  - Photoepilation (laser and intense pulsed light [IPL]): hair follicles destroyed by wavelengths of light absorbed by melanin. Good for pigmented hair; laser treatment is more effective than shaving, waxing, and electrolysis. It lasts 3 to 6 months as vellus follicles remain and can be converted to terminal pigmented hair under excess androgens.
- To endocrinologist if difficulty in determining diagnosis, achieving therapeutic goals, or resistant to first-line therapies. Pre-pubertal and postmenopausal hirsutism is suspicious for neoplastic or secondary endocrine causes and should be referred for further evaluation.
- Consider referral or consultation for following therapies:

- Cosmetic: permanent. Electrolysis: destroys individual hair follicles. May be expensive and time consuming.

**ACUTE GENERAL Rx**

See "Pharmacologic Therapy."

**CHRONIC Rx**

See "Pharmacologic Therapy."

**PHARMACOLOGIC THERAPY**

- Usually second-line treatment following non-pharmacologic, physical methods of hair control, and in consideration of patient's comorbidities and risk factors, patient preferences, area of excess hair amenable to treatment, and access and affordability of treatments.
- Pharmacologic treatments categorized as topical, oral contraceptive pills (OCPs), anti-androgens (potential adverse effects on a developing male fetus, so use with reliable contraception), other treatments directed at specific underlying etiology.
- Topical: Eflornithine topical cream 13.9%: unclear mechanism of action; may inhibit ornithine decarboxylase, retarding hair growth. Temporary cosmetic treatment for facial hair. Applied directly to unwanted facial hair bid with at least 8 hr spaced applications. Does not remove hair, rather slows growth. Slow response over 4 to 8 wk. Hair growth returns upon discontinuation of treatment.
- OCPs: Suppress ovarian steroidogenesis and LH through low-dose estrogen and low androgenic progestational agents. Slow response to treatment. Suppresses new hair growth. Established hair unaffected. Low-dose OCPs with low androgenic progestational agents, for example, desogestrel, drospirenone, norgestimate. Avoid norgestrel and levonorgestrel (higher androgenic progestational agents).
- Antiandrogens: Spironolactone: when OCPs unacceptable or may be added for disappointing results after 6 mo of OCP treatment.
  - Aldosterone-antagonist diuretic inhibits adrenal and ovarian biosynthesis of androgens. May result in ovulation, so consider contraception needs.
  - Slow response usually 6 mo or more.
  - 200 mg PO qd, then decrease to 25 to 50 mg qd maintenance.
  - May cause hyperkalemia.
  - Anovulatory, unopposed estrogen states require progestin management.

**REFERRAL**

- To endocrinologist if difficulty in determining diagnosis, achieving therapeutic goals, or resistant to first-line therapies. Pre-pubertal and postmenopausal hirsutism is suspicious for neoplastic or secondary endocrine causes and should be referred for further evaluation.
- Consider referral or consultation for following therapies:

1. Finasteride: antiandrogen, in hair follicle blocks  $5\alpha$ -reductase conversion of testosterone to intranuclearly active  $5\alpha$ -dihydrotestosterone (DHT).
  1. Use only with reliable contraception because DHT necessary for normal male fetus urogenital development.
  2. Not FDA approved for treatment of hirsutism.
  3. 1 to 5 mg PO qd.
2. Flutamide: inhibits androgen uptake and receptor binding
  1. Not recommended by Endocrine Society Clinical Practice Guidelines and not FDA approved for treatment of hirsutism, but used by some European endocrinologists.
  2. Use only with reliable contraception.
  3. Reserved for women with severe, resistant hirsutism because of risk of hepatic dysfunction.
  4. 250 mg PO bid.
3. Cyproterone acetate (not available in the United States): antiandrogen that com-

petes with DHT for binding androgen receptors. Used as progestin component of OCPs outside the United States.

- Other treatments directed at specific underlying etiology:
  1. Metformin/thiazolidinediones: therapy reserved for documented insulin-resistant states.
  2. GnRH agonists: recommended only in women with severe hyperandrogenemia (e.g., ovarian hyperthecosis) with suboptimal response to combination low-dose estrogen/progestin pills and antiandrogen treatment. Inhibits gonadotropin and consequently ovarian androgen and estrogen secretion.
  3. Dexamethasone: adrenal glucocorticoid suppression is reserved for diagnosis of adrenal enzyme deficiency.
  4. Total abdominal hysterectomy/bilateral salpingo-oophorectomy reserved for recalcitrant hirsutism in older female with hyperthecosis and undesired fertility.

## PEARLS & CONSIDERATIONS

### COMMENTS

- Hirsutism is both an endocrine and cosmetic problem for patients.
- Ovulation induction therapy is indicated in women desiring pregnancy.
- Delay checking serum androgens until oral contraceptives have been discontinued for 2 to 3 mo.
- Evaluation of incidental adrenal mass is always warranted.

### SUGGESTED READINGS

Available at [www.expertconsult.com](http://www.expertconsult.com)

### RELATED CONTENT

Hirsutism (Patient Information)

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## BASIC INFORMATION

### DEFINITION

Histiocytosis X, now known as Langerhans cell histiocytosis (LCH), is a rare disorder characterized by the abnormal proliferation of pathologic Langerhans cells. These dendritic cells form characteristic infiltrates with eosinophils, lymphocytes, and other histiocytes found in various organs.

### SYNOMYMS

Eosinophilic granuloma  
Hand-Schüller-Christian disease  
Letterer-Siwe disease  
Langerhans cell histiocytosis  
Langerhans cell granulomatosis  
Diffuse reticuloendotheliosis

### ICD-9CM CODES

202.5 Acute histiocytosis X  
277.89 Chronic histiocytosis X

### ICD-10CM CODES

C96.0 Multifocal and multisystemic (disseminated) Langerhans-cell histiocytosis  
C96.6 Unifocal Langerhans-cell histiocytosis  
D76.3 Other histiocytosis syndromes  
C96.5 Multifocal and unisystemic Langerhans-cell histiocytosis

### EPIDEMIOLOGY & DEMOGRAPHICS

- LCH is mainly a childhood disorder with a peak incidence from age 1 to 4 yr.
- The annual incidence in the pediatric population is 2 to 5 per million.
- LCH affects males more often than females, 2:1.
- Pulmonary LCH (a localized form more commonly found in adults) has an equal male/female incidence, if not female predominance, possibly because of increased prevalence of smoking in women.
- More common in Caucasians.
- Disseminated LCH usually occurs before 2 yr of age.

### PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Clinical presentation is variable, and ranges from:
  - A benign isolated bony lesion (eosinophilic granuloma), most often found in children younger than 15 yr of age.
  - Multiple bone lesions with soft tissue gingival and oral mucosal involvement (Hand-Schüller-Christian disease); generally occurs in children younger than 10 yr of age.
  - An aggressive disseminated disease infiltrating organs and causing organ dysfunction (Letterer-Siwe disease). This is the rarest form of LCH, affecting mostly children younger than 2 yr.
- Bone lesions (80% to 100%).
  - May be isolated or multiple.

- Painful, often worse at night.
- Skull most often involved, followed by long bones; lesions rarely seen in small bones of hands and feet.
- Proptosis.
- Mastoiditis.
- Loose teeth.
- Gingival hypertrophy.
- Skin is involved in >80% of patients with disseminated disease and in 30% of patients with less extensive disease.
  - Seborrhea-like scaling of scalp, petechial and purpuric lesions, ulcers, and bronzing of the skin may occur.
  - Common sites: scalp, neck, trunk, groin, and extremities.
- Lymphadenopathy (10%): cervical and inguinal.
- Pulmonary disease is very frequent in adults (usually as isolated disease), but can be seen in 23% to 50% of children as well. Lung involvement always occurs as part of the disseminated disease in children.
- Pulmonary involvement may manifest with cough, tachypnea, cyanosis, inspiratory crackles, pleural effusions, or pneumothorax. Diffuse emphysema associated with pulmonary fibrosis is the end stage of a mixed restrictive and obstructive pattern of disease.
- Liver involvement manifesting as hepatomegaly with or without jaundice (50% to 60%).
- Involvement of the biliary tree may be seen as biliary fibrosis or sclerosing cholangitis.
- Splenomegaly (5%).
- CNS involvement occurs in 25% to 35% of patients, most often in those with disseminated disease. The most common cerebral site affected is the hypothalamic-neurohypophyseal region, where infiltration and destruction usually result in diabetes insipidus with insatiable thirst and urination. The second most common site of involvement is the cerebellum.
- Involvement of the thymus, parotid glands, and GI tract has been reported in rare cases.

### ETIOLOGY

- The etiology of LCH is unknown, though multiple theories have been proposed.
- Some degree of genetic predisposition has been proposed and recent evidence suggests LCH as a monoclonal proliferative neoplastic disorder in children.
- In adults, pulmonary LCH appears to be primarily an immune-mediated reactive process and has been linked to cigarette smoking. Cigarette smoke had not been observed as a causative factor in other forms of LCH.

## Dx DIAGNOSIS

Tissue biopsy of organ lesions reveals pathologic Langerhans cells characterized by the presence of multiple surface nucleoproteins including CD1a, the presence of which establishes definitively histologic diagnosis of LCH. The infiltration by eosinophils forming pseudo-abscesses is characteristic.

### DIFFERENTIAL DIAGNOSIS

The differential diagnosis of histiocytosis syndromes is extensive, including all causes of diabetes insipidus, lytic bone lesions, dermatitis, hepatomegaly, and lymphadenopathy. In regards to histiocytosis syndromes of childhood, there are three classes based on histopathologic findings. Class I histiocytosis (also known as LCH) includes the clinical entities of eosinophilic granuloma, Hand-Schüller-Christian disease, and Letterer-Siwe disease. Class II histiocytoses are non-malignant proliferative disorders that are characterized by accumulation of macrophages. The two major diseases among the class II histiocytoses are hemophagocytic lymphohistiocytosis (HLH) and infection-associated hemophagocytic syndrome (IAHS). These diseases are grouped together under the term *hemophagocytic lymphohistiocytosis* (HLH) (see Table EH1-24). Class III histiocytoses are

**TABLE EH1-24** Distinguishing Characteristics of the Reactive Lymphohistiocytoses

	Genetic History	Virus Infection	Cellular Immune Function	Miscellaneous
HLH, genetic	Autosomal recessive	Possibly associated	↓ CMI ↓ NK cell activity ↓ Monocyte killing ↓ CMI	Perforin deficiency Hypertriglyceridemia, Perforin (PRF1), Munc 13-4 mutations
Secondary infection-associated	Sporadic	Yes	↓ CMI NL or ↑ NK cell in instances associated with EBV ↓ Anomalous EBV-related killing	Coagulopathy early in the course of the disease
XLP	X-linked sporadic	EBV	NL or ↑ NK cell NL or ↑ anomalous EBV-related killing	SH2D1A mutation Severe, often fatal hepatitis
SHML	Sporadic	?EBV	Not reported	Autoimmune phenomena
LG	Sporadic	EBV	↓ CMI	Lymphoma development

CMI, Cell-mediated immunity; EBV, Epstein-Barr virus; HLH, hemophagocytic lymphohistiocytosis; LG, lymphomatoid granulomatosis; NK, natural killer; NL, normal; SHML, sinus histiocytosis with massive lymphadenopathy; XLP, X-linked lymphoproliferative syndrome. From Nathan DG et al (eds): *Nathan and Oski's hematology of infancy and childhood*, ed 6, Philadelphia, 2003, Saunders.

malignancies of cells of monocyte-macrophage lineage (acute monocytic leukemia) and true malignant histiocytoses.

## WORKUP

Baseline evaluation should include bone scan, chest x-ray, skeletal x-ray, abdominal ultrasound, and routine laboratory tests to assess the extent of disease involvement.

## LABORATORY TESTS

- CBC is not specific but may reveal cytopenias in patients with bone marrow involvement.
- Electrolytes, BUN, creatinine, urinalysis, and urine and serum osmolality are helpful in the diagnosis of diabetes insipidus during fluid deprivation testing.
- Liver function tests (LFTs) may be elevated in patients with liver involvement.
- Bronchoalveolar lavage may show increased numbers of CD1a-positive histiocytes or Langerhans cells in patients with pulmonary LCH.

## IMAGING STUDIES

- Radiograph studies of affected areas show lytic lesions with or without sclerotic margins.
- Radiograph bone survey is done searching for other lesions.
- Bone scan complements the bone survey studies.
- Panoramic dental view of the mandible and maxilla for children with oral involvement.
- Chest radiograph can show interstitial reticulonodular infiltrates. This pattern typically progresses toward frank honeycombing fibrosis later in the course of the disease (Fig. EH1-53).
- High-resolution CT scan of the chest confirms interstitial lung scarring, nodules, and cysts, and represents an excellent noninvasive means for diagnosis and follow-up of pulmonary LCH. Pulmonary cysts are bilateral and symmetric, showing slight upper-lobe predominance with relative sparing of the costophrenic angles.
- CT scans of the temporal bone searching for mastoid, and inner and middle ear involvement.
- Ultrasound of the abdomen may show hepatosplenomegaly.
- Conventional cholangiography or MRI cholangiopancreatography can confirm the pres-

ence of disease in patients suspected to have biliary involvement.

- MRI of the brain to visualize the hypothalamic-hypophyseal region in patients suspected of having diabetes insipidus.

## RX TREATMENT

Treatment is still evolving and is based on organ involvement and the extent of disease.

### ACUTE GENERAL Rx

Isolated bone lesions can be treated by:

- Curettage of affected site and implantation of allograft bone chips or polymethylmethacrylate.
- Intralesional prednisone or prednisone and vinblastine.
- Bisphosphonates.
- NSAIDs.
- Radiation therapy is useful only for bone lesions of the vertebrae or femoral neck at risk of collapse.

Single skin lesions are treated with:

- Topical steroid (e.g., triamcinolone acetonide) applied bid.
  - Nitrogen mustard in 20% solution.
  - Surgery.
  - Intralesional interferon.
  - Isotretinoin.
- Treatment of solitary lymph node involvement:
- Excision at the time of diagnosis.
  - Systemic oral prednisone.
- Treatment for multiple bone lesions, skull base lesions, or multisystem disease includes:
- Vinblastine 6 mg/m<sup>2</sup> IV bolus every wk for 6 mo or etoposide 150 mg/m<sup>2</sup> IV for 3 days every 3 wk for 6 mo and oral prednisone for 6 mo.

### CHRONIC Rx

- For severe, high-risk, disseminated cases not responding within 6 wk of initial treatment, salvage therapy, including high dose of the purine analogue cladribine along with high-dose cytosine arabinoside followed by allogeneic blood stem cell transplantation, should be considered. Additionally, liver or lung transplantation might be the treatment of choice for terminal liver and lung failure patients.
- Diabetes insipidus is treated with DDAVP 0.1 to 0.8 mg PO or 1 nasal spray bid to tid.

- Adults with isolated pulmonary LCH do not require aggressive treatment and will benefit from smoking cessation.

- Empirical use of steroids, in either short pulses or longer exposures, has also been suggested in the treatment of pulmonary disease; however, data regarding effectiveness are still limited.

- Lung transplantation has been tried in both children and adults with advanced pulmonary disease and limited lung function, but failure rates are high because of local recurrence after transplantation.

## DISPOSITION

- Patients with disease localized to only one organ system have a good prognosis and appear to need minimal, if any, treatment. For patients with isolated pulmonary LCH, the 5-yr survival rate is around 80%.
- Patients with disseminated disease have an increased risk for poor outcome, with a reported mortality rate of 10% to 20%, and 50% risk of life-imparing morbidity. A poor prognostic feature is the failure to respond to therapy in the first 6 wk.
- In patients with disseminated LCH and <2 yr of age, the mortality rate is 30%.

## REFERRAL

Multidisciplinary approach: pediatric oncologist, radiation oncologists, oral maxillary surgeons, ear-nose-throat specialists, audiology, dermatology, endocrinology, and family counseling.

## PEARLS & CONSIDERATIONS

### COMMENTS

- The course of LCH is often unpredictable and varies from spontaneous resolution to rapid progression and death, or multiple recurrences and regressions with risk for permanent sequelae.
- The association of LCH with other malignancies (e.g., acute lymphocytic leukemia, acute nonlymphoblastic leukemia, and solid tumors) has been cited.

### PREVENTION

Effective antismoking measures may prevent pulmonary LCH.

### PATIENT & FAMILY EDUCATION

- Instruct patients to promptly report the development of hemoptysis. This symptom may indicate malignancy or superimposed bacterial/fungal infection, such as *Aspergillus* species infection.
- Educate about the likely etiologic role of cigarette smoking.

## SUGGESTED READINGS

Available at [www.expertconsult.com](http://www.expertconsult.com)

AUTHOR: MARK F. BRADY, M.D., M.P.H., M.M.S.



**FIGURE EH1-53 Langerhans cell histiocytosis (LCH; histiocytosis X).** There is a reticular nodular pattern in the upper lobes. The lung volumes are preserved. (From McLoud TC [ed]: *Thoracic radiology, the requisites*, St Louis, 1998, Mosby.)

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## BASIC INFORMATION

### DEFINITION

Histoplasmosis is caused by the fungus *Histoplasma capsulatum* and characterized by a primary pulmonary focus with occasional progression to chronic pulmonary histoplasmosis (CPH) or various forms of dissemination. Progressive disseminated histoplasmosis (PDH) may present with a diverse clinical spectrum, including adrenal necrosis, pulmonary and mediastinal fibrosis, and ulcerations of the oropharynx and GI tract. In those patients coinfected with HIV, it is a defining disease for AIDS.

### SYNOMYMS

North American histoplasmosis  
Ohio Valley fever  
Vanderbilt disease

#### ICD-9CM CODES

- 115.90 Histoplasmosis
- 115.94 Histoplasmosis with endocarditis
- 115.91 Histoplasmosis with meningitis
- 115.93 Histoplasmosis with pericarditis
- 115.95 Histoplasmosis with pneumonia
- 115.92 Histoplasmosis with retinitis

#### ICD-10CM CODES

- B39.9 Histoplasmosis, unspecified
- B39.9 with: I39 Endocarditis and heart valve disorders in diseases classified elsewhere
- B39.9 with: G02 Meningitis in other infectious and parasitic diseases classified elsewhere
- B39.9 with: I32 Pericarditis in diseases classified elsewhere
- B39.9 with: J17 Pneumonia in diseases classified elsewhere
- B39.9 with: H32 Chorioretinal disorders in diseases classified elsewhere

### EPIDEMIOLOGY & DEMOGRAPHICS

#### INCIDENCE (IN U.S.):

- Unknown for acute pulmonary disease
- For CPH, estimated at 1/100,000 cases in endemic areas
- For PDH in immunocompetent adults, estimated at 1/2000 cases of histoplasmosis

#### PREVALENCE:

Unknown

**PREDOMINANT SEX:** Clinically evident disease is most common in males; male/female ratio of 4:1

#### PREDOMINANT AGE:

- CPH is most often seen in males >50 yr old with an associated history of COPD.
- Presumed ocular histoplasmosis syndrome (POHS) is seen between ages of 20 and 40 yr.

#### PEAK INCIDENCE:

Unknown

### PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Conidia are deposited in alveoli then converted to yeast forms where they spread to regional lymph nodes and other organs, especially liver and spleen.

- 1 to 2 wk later, a granulomatous inflammatory response begins to contain the yeast in the form of discrete granulomas.
- Delayed-type hypersensitivity to *Histoplasma* antigens occurs 3 to 6 wk after exposure.
- Clinical disease manifests in various forms, depending on host cellular immunity and inoculum size:
  - 1. Acute primary pulmonary histoplasmosis
    - a. An overwhelming number of patients are asymptomatic.
    - b. Most clinically apparent infections manifest by complaints of fever, headache, malaise, pleuritic chest pain, nonproductive cough, and weight loss.
    - c. Less than 10%, mainly women, complain of arthralgias, myalgias, and skin manifestations such as erythema multiforme or erythema nodosum.
    - d. Acute pericarditis presents in a smaller percentage of patients.
    - e. Hepatosplenomegaly is most commonly observed in children.
    - f. With particularly heavy exposure, there is severe dyspnea, marked hypoxemia, impending respiratory failure.
    - g. Most patients are asymptomatic within 6 wk.
  - 2. CPH
    - a. Presents insidiously with low-grade fever, malaise, weight loss, cough, sometimes with blood-streaked sputum or frank hemoptysis.
    - b. Most patients with cavitary lesions present with associated COPD or chronic bronchitis, masking underlying fungal disease.
    - c. Tends to worsen preexisting pulmonary disease and further contribute to eventual respiratory insufficiency.
  - 3. PDH
    - a. In both acute and subacute forms, constitutional symptoms of fever, fatigue, malaise, and weight loss are common.
    - b. Acute form (seen in infants and children) presents with respiratory symptoms, fever  $\geq 101^{\circ}$  F ( $38.3^{\circ}$  C), generalized lymphadenopathy, marked hepatosplenomegaly, and fulminant course resembling septic shock associated with a high fatality rate.
    - c. Subacute form is more common in adults and associated with lower temperatures, hepatosplenomegaly, oropharyngeal ulceration, focal organ involvement (including adrenal destruction, endocarditis, chronic meningitis, and intracerebral mass lesions).
    - d. Course of subacute form is relentless, with untreated patients dying within 2 yr.
    - e. Chronic PDH is found in adults and marked by gradual symptoms of weight loss, weakness, easy fatigability; low-grade fever when present; oropharyngeal ulcerations and hepatomegaly and/or splenomegaly in one third of patients.
    - f. Less clinical evidence of focal organ involvement in chronic form than in subacute form.
    - g. Natural history of chronic form is protracted and intermittent, spanning months to years.
- Histoplasmoma
  - 1. A healed area of caseation necrosis surrounded by a fibrous capsule
  - 2. Usually asymptomatic
- Mediastinal fibrosis
  - 1. A rare consequence of a fibroblastic process that encases caseating mediastinal lymph nodes producing severe retraction, compression, and distortion of mediastinal structures
  - 2. Constriction of the bronchi resulting in bronchiectasis, also esophageal stenosis associated with dysphagia, and superior vena cava syndrome
- POHS
  - 1. Diagnosis characterized by distinct clinical features, including atrophic choroidal scars and maculopathy in patients with histories suggestive of exposure to the fungus (e.g., residence in an endemic area)
  - 2. Patient complains of distortion or loss of central vision without pain, redness, or photophobia
  - 3. Usually no evidence of infection except for a positive skin reaction to histoplasmin
- In patients with AIDS
  - 1. Possible presentation as overwhelming infection similar to acute PDH seen in children
  - 2. Constitutional symptoms: fever, weight loss, malaise, cough, dyspnea
  - 3. About 10% with cutaneous maculopapular, erythematous eruptions or purpuric lesions on face, trunk, and extremities
  - 4. Up to 20% with CNS involvement, manifesting as intracerebral mass lesions, chronic meningitis, or encephalopathy

### ETIOLOGY

- *H. capsulatum* is a dimorphic fungus present in temperate zones and river valleys worldwide.
- In the U.S., it is highly endemic in southeastern, mid-Atlantic, and central states.
- Exists as mold at ambient temperature and favors soils enriched with bird or bat droppings.

## Dx DIAGNOSIS

### DIFFERENTIAL DIAGNOSIS

- Acute pulmonary histoplasmosis
  - 1. *Mycobacterium tuberculosis*
  - 2. Community-acquired pneumonias caused by *Mycoplasma* and *Chlamydia*
  - 3. Other fungal diseases, such as *Blastomyces dermatitidis* and *Coccidioides immitis*
- Chronic cavitary pulmonary histoplasmosis: *M. tuberculosis*
- Histoplasmomas: true neoplasms

### WORKUP

- Suspect diagnosis in patients who present with a history of residence or travel in an endemic

area, especially if engaged in occupations (e.g., outside construction or street cleaning) or hobbies (e.g., cave exploring) that increase the likelihood of exposure to fungal spores.

- Suspect diagnosis in immunosuppressed patients with remote history of exposure, especially if associated with characteristic calcifications on chest x-ray.

## LABORATORY TESTS

- Demonstration of organism on culture from body fluid or tissues biopsy (Fig. EH1-54) to make definitive diagnosis
  - Especially high yield in patients with AIDS
  - Characteristic oval yeast cells in neutrophils with Giemsa stain from peripheral smear
  - Preparations of infected tissue with Gomori's silver methenamine for revealing yeast forms, especially in areas of caseation necrosis
- Serologic tests, including complement-fixing (CF) antibodies and immunodiffusion assays
- Detection of *Histoplasma* antigen in urine: may be influenced by infections with *Blastomyces* and *Coccidioides*
- In PDH
  - Pancytopenia
  - Marked elevations in alkaline phosphatase and alanine aminotransferase (ALT) common
- In chronic meningitis (majority of cases)
  - CSF pleocytosis with either lymphocytes or neutrophils predominating
  - Elevated CSF protein levels
  - Hypoglycorrachia

## IMAGING STUDIES

- Chest radiograph examination in acute pulmonary histoplasmosis
  - Singular or multiple patchy infiltrates, especially in the lower lung fields
  - Hilar or mediastinal lymphadenopathy with or without pneumonitis
  - Diffuse nodular or confluent bilateral miliary infiltrates characteristic of heavier exposure
  - Infrequent pleural effusions, except when associated with pericarditis
- Chest radiograph examination in histoplasmosis: coin lesion displaying central calcification, ranging from 1 to 4 cm in diameter, predominantly located in the subpleural regions
- Chest radiograph examination in CPH (Fig. EH1-55):
  - Upper lobe disease frequently associated with cavities
  - Preexisting calcifications in the hilum associated with peribronchial streaking extending to the parenchyma

- Chest radiograph examination in acute PDH: hilar adenopathy and/or diffuse nodular infiltrates
- CT scan of adrenals to reveal bilateral enlargement and low-attenuation centers

## Rx TREATMENT

### NONPHARMACOLOGIC THERAPY

For life-threatening disease seen in acute disseminated disease or infection in patients with AIDS: supportive therapy with IV fluids

### ACUTE GENERAL Rx

- No drug therapy is required for asymptomatic pulmonary disease.
- A course of therapy with itraconazole 200 mg PO tid for 3 days, then 200 mg/day PO for 6-12 wk may be beneficial in some patients with acute pulmonary distress. Avoid fluconazole because it is not as active.
- Same therapy appropriate for immunocompetent, mild to moderately symptomatic patients with CPH and subacute and chronic forms of PDH, but duration for 6 to 12 mo.
- Use amphotericin B 0.7 to 1 mg/kg IV q day for initial therapy in moderate to severe disease and then transition to oral itraconazole within 1-2 wk. Lipid formulations of amphotericin can be used to avoid nephrotoxicity of amphotericin B.
- (Liposomal amphotericin: 3mg/kg/day IV or amphotericin B lipid complex: 5 mg/kg/ day)
- Posaconazole and voriconazole are highly effective as well, but echinocandins such as micafungin are not effective.
- Chronic cavitary pulmonary histoplasmosis: itraconazole 200 mg PO tid for 3 days, then once or twice daily for at least 12 mo.
- CNS histoplasmosis: liposomal amphotericin B, 5 mg/kg/day for a total of 175 mg/kg over 4-6 wk, then itraconazole 200 mg 2-3×/day for at least 12 mo.
- Endocarditis: surgical treatment with excision of infected valve or graft combined with amphotericin for a total dose of 35 mg/kg or 2.5 g.
- For pericardial disease:
  - Antifungal therapy: no apparent benefit
  - Best managed with NSAIDs
- For POHS:
  - Antifungal therapy: no apparent benefit
  - May respond to laser therapy

### CHRONIC Rx

- In patients with AIDS: lifelong suppressive therapy with either itraconazole, given 200 mg PO q day, or IV amphotericin B at a dose of 50 mg once weekly; a triazole compound posaconazole (400 mg PO bid) may be useful in refractory cases, but clinical experience is limited at this point.
- Prophylaxis in HIV-infected patients with <150 CD4 cells/mm<sup>3</sup>: itraconazole 200 mg PO qd

### DISPOSITION

For those with chronic or progressive disease, especially if immunocompromised, prognosis is dependent on prompt recognition and timely administration of appropriate antifungal drugs.

### REFERRAL

- To an infectious disease specialist in suspected cases of disseminated disease, especially if immunocompromised
- To a pulmonologist for patients with CPH form because of progressive respiratory compromise
- To a thoracic surgeon for decompression procedures for progressive mediastinal fibrosis

## PEARLS & CONSIDERATIONS

- H. capsulatum*, variety *duboisii*, also known as African histoplasmosis, is restricted to Senegal, Nigeria, Zaire, and Uganda.
- Unlike *H. capsulatum*, pulmonary forms of *duboisii* are not seen, and the disease is limited to the skin, soft tissues, and bone.

### COMMENTS

- Patients living in endemic areas, especially if immunocompromised, should take appropriate respiratory precautions when disposing of bird waste from rooftop or home aviaries.
- Appropriate respiratory precautions should also be taken when leisure traveling to areas that act as a natural haven for the fungus, such as bat caves.

### SUGGESTED READINGS

Available at [www.expertconsult.com](http://www.expertconsult.com)

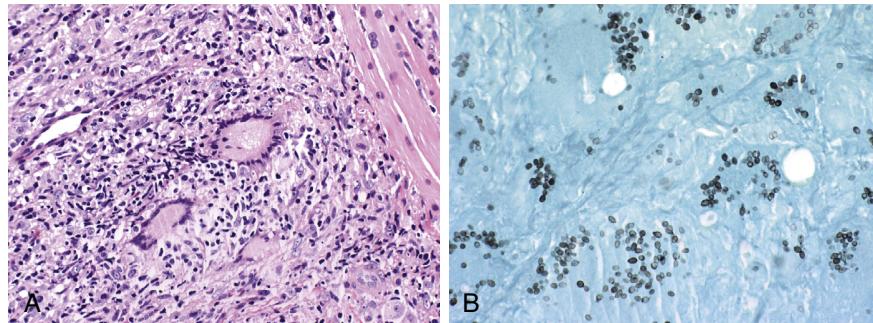
### RELATED CONTENT

Histoplasmosis (Patient Information)

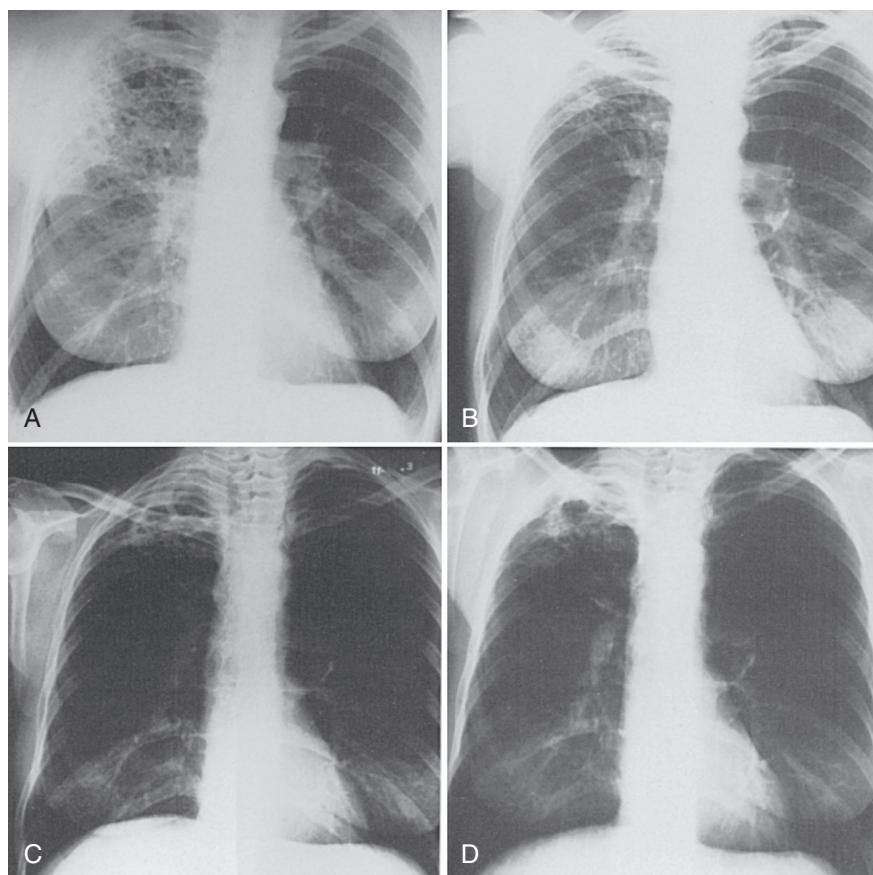
AUTHOR: GLENN G. FORT, M.D., M.P.H.

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**FIGURE EH1-54** **A**, Photomicrograph shows a tissue biopsy specimen from a patient with slowly progressing disseminated histoplasmosis. Granulomas are well formed, and no organisms are seen. (Hematoxylin and eosin stain  $\times 450$ .) **B**, Special stains better demonstrate yeast in tissue sections. (Silver methenamine stain;  $\times 450$ .) (From Mason, RJ: *Murray & Nadel's textbook of respiratory medicine*, 5th ed, Philadelphia, 2010, Saunders.)



**FIGURE EH1-55** The evolution of chronic pulmonary histoplasmosis in a smoker. **A**, At the onset of the illness, the chest radiograph shows multiple cavity-like air spaces. **B**, Two and one-half years later, fibrosis has occurred with volume loss of the lobe and retraction of the hilum. **C**, A further 17 months later, the entire right upper lobe appears destroyed. **D**, There are signs of continued activity and a residual cavity at the time of diagnosis. The sputum culture was positive for *Histoplasma capsulatum*. (From Mason, RJ: *Murray & Nadel's textbook of respiratory medicine*, 5th ed, Philadelphia, 2010, Saunders.)



## BASIC INFORMATION

### DEFINITION

Patients with histrionic personality disorder present with a pervasive pattern of excessive emotionality and attention-seeking behavior that generally begins in early adulthood.

### SYNOMYS

Hysterical personality disorder  
Psycho-infantile personality disorder  
Personality disorder (nonspecific)  
Personality disorder (trait specified)

### ICD-9CM and DSM-5 CODES

301.50 Histrionic personality disorder,  
unspecified

### ICD-10CM CODES

F60.4 Histrionic personality disorder

### EPIDEMIOLOGY & DEMOGRAPHICS

#### PREVALENCE (IN U.S.):

- Diagnosed more often in women (85%); rarely found in men.
- Prevalence: 1% to 3%.

**PREDOMINANT SEX:** Female. Cultural factors (e.g., attention-seeking behavior not as acceptable in men) may lead to more common diagnosis in women.

**PREDOMINANT AGE:** Generally begins in early adulthood.

**GENETICS:** Limited research using interview and self-report methods suggests histrionic personality disorder has a moderate genetic component.

### PHYSICAL FINDINGS & CLINICAL PRESENTATION

Features include five or more of the following:

- Is uncomfortable in situations where he or she is not the center of attention.
- Interaction with others is often characterized by inappropriate sexually seductive or provocative behavior.
- Displays rapidly shifting and shallow expression of emotions.
- Consistently uses physical appearance to draw attention to self.
- Has a style of speech that is excessively impressionistic and lacking in detail.
- Shows self-dramatization, theatricality, and exaggerated expression of emotion.

- Is suggestible (i.e., easily influenced by others or circumstances).
- Considers relationships to be more intimate than they actually are.

### ETIOLOGY

- Unknown.
- Hypothesized that childhood events, psychosocial adversity, and genetics are contributory.

## Dx DIAGNOSIS

### DIFFERENTIAL DIAGNOSIS

- Narcissistic and borderline personality disorders share common features.
- Other personality disorders (e.g., antisocial personality disorder, dependent personality disorder)
- Personality change attributable to general medical condition.
- Symptoms in association with chronic substance abuse.

### WORKUP

There is no formal test to establish diagnosis.

## Rx TREATMENT

### NONPHARMACOLOGIC THERAPY

- Long-term individual psychotherapy is treatment of choice.
- No controlled psychotherapy studies.
- Unlike other people who have personality disorders, these individuals often seek treatment and exaggerate their symptoms and difficulties in functioning.
- Patients tend to be more emotionally needy and are often reluctant to terminate therapy.

### ACUTE GENERAL Rx

- No placebo-controlled trials.
- Care should be given when prescribing medications because of the potential for self-destructive or otherwise harmful behaviors.

### DISPOSITION

- Therapeutic approaches should not focus on the long-term personality change, but rather short-term alleviation of specific difficulties and deficits within the person's life.

- Therapeutic approaches that emphasize vague somatic, anxious, or depressive symptoms often fail.
- Patients are likely to be intolerant or drop out of treatment approaches that use delayed gratification.
- Symptoms are moderately stable over adulthood and may remit or decrease in intensity with age.

### REFERRAL

Primarily treated by mental health professionals.

## PEARLS & CONSIDERATIONS

- This disorder is difficult to treat.
- Like most personality disorders, patients present for treatment only when stress or other situational factors within their lives have made their ability to function and cope effectively impossible.
- Suicidality should be assessed on a regular basis, and suicidal threats and self-mutilation should not be ignored or dismissed.
- An alternative model in DSM-5 section III reconceptualizes histrionic personality disorder as "Personality Disorder, Trait Specified," which rates: (1) impairment in personality functioning (identity, self-direction, empathy, and/or intimacy) and (2) pathologic trait domains such as attention seeking, grandiosity, and manipulativeness.

### PATIENT & FAMILY EDUCATION

Group and family therapy approaches are generally not recommended because individuals with this disorder often try to draw attention to themselves and exaggerate every action and reaction.

### SUGGESTED READINGS

Available at [www.expertconsult.com](http://www.expertconsult.com)

AUTHORS: MARK ZIMMERMAN, M.D., and THERESA A. MORGAN, PH.D., M.PHIL.

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## BASIC INFORMATION

- HIV cognitive dysfunction covers a spectrum of disorders ranging from asymptomatic to clinically severe (including AIDS dementia complex or HIV encephalopathy).
- Cognitive, motor, and behavioral abnormalities

### SYNONYMS

HIV-associated neurocognitive disorder

#### ICD-9CM CODES

042 (for diseases related to HIV; no particular code for HIV cognitive dysfunction)

#### ICD-10CM CODES

B20 Human immunodeficiency virus [HIV] disease

R41.8 Other and unspecified symptoms and signs involving cognitive functions and awareness

### EPIDEMIOLOGY

- Presenting complaint in only 3% of cases
- Incidence: reduced from 60% to 1% since introduction of HIV treatment; however, as more HIV-infected patients live longer, prevalence may be increasing.
- Minor cognitive disorders are more common and seen in 20% of patients; not necessarily progressive
- Rarely precedes clinical evidence of HIV infection

### CLINICAL FEATURES

- Cognitive changes: forgetfulness, poor attention and concentration, increased difficulty performing complex tasks, slowed psychomotor speed

- Behavioral changes: apathy, lack of initiative, social withdrawal, irritability, occasionally agitation, psychosis or obsessive compulsive disorder
- Motor problems: clumsiness, unsteady gait, poor balance, tremor, leg weakness
- Progressive/later stages: bedbound, severe dementia, bowel/bladder incontinence
- Subcortical dementia (aphasia, apraxia, and agnosia) is uncommon
- Results from inflammation triggered by HIV itself (not related to opportunistic infection) and immune activation of microglia and brain macrophages
- Clinically may resemble Parkinson's disease
- In children: developmental delay, microcephaly, and spasticity are common

- Potential causes for cognitive impairment that must be ruled out include:
  - Opportunistic infections (toxoplasmosis, CNS lymphoma)
  - Vitamin B<sub>12</sub> deficiency
  - Substance use
  - Organic affective disorder (such as depression and mania)
  - Side effects of prescribed medications



## TREATMENT

Early treatment with antiretroviral therapy (ART) leads to clinical improvement.



## PEARLS & CONSIDERATIONS

- Initiation of ART can lead to rapid improvement in cognitive function in early stages (untreated, life span is typically 4 to 6 mo)
- Most common presenting complaint in children infected with HIV
- Mini-mental status examination (MMSE): baseline scores in HIV patients are very helpful
- Usually cognitive symptoms precede motor abnormalities
- Four HIV-related opportunistic infections that commonly cause cognitive impairment are: toxoplasmosis, cryptococcal meningitis, progressive multifocal leukoencephalopathy, and CNS lymphoma

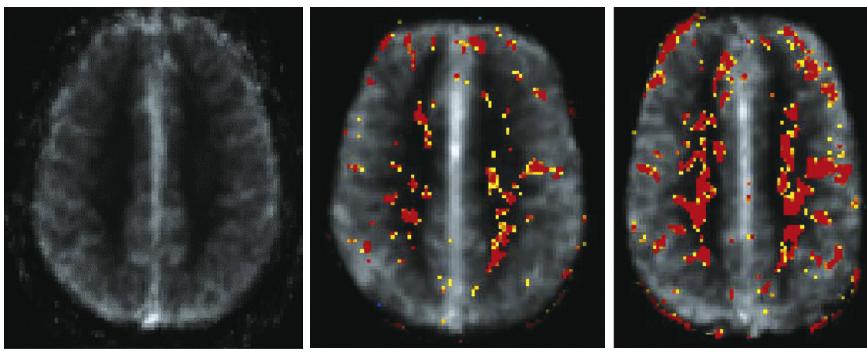
### REFERRALS

- Upon diagnosis/clinical suspicion for HIV-associated cognitive dysfunction, referral to neurology is recommended
- Referral to neuropsychology may be considered

### SUGGESTED READINGS

Available at [www.expertconsult.com](http://www.expertconsult.com)

AUTHOR: DIVYA SINGHAL, M.D.



**FIGURE H1-56** Perfusion MRI (pMRI) maps showing regions of increasing cerebral blood volume (CBV) with advancing HIV groups: asymptomatic, minor cognitive-motor disorder (MCMD), and HIV-associated dementia (HAD). Areas of red indicate  $>2$  standard deviations elevation in CBV. (Tucker KA et al: Neuroimaging in human immunodeficiency virus infection. *J Neuroimmunol* 157(1–2): 153–162, 2004.)

## SUGGESTED READINGS

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## BASIC INFORMATION

### DEFINITION

Hodgkin's lymphoma is a malignant disorder of lymphoreticular origin, characterized histologically by the presence of multinucleated giant cells (Reed-Sternberg cells) usually originating from B lymphocytes in germinal centers of lymphoid tissue.

#### ICD-9CM CODES

- 201.9 Hodgkin's lymphoma, unspecified
- 201.0 Hodgkin's paragranuloma
- 201.4 Hodgkin's lymphoma, lymphocyte predominance
- 201.5 Hodgkin's lymphoma, nodular sclerosis
- 201.6 Hodgkin's lymphoma, mixed cellularity
- 201.6 Hodgkin's lymphoma, mixed cellularity
- 201.7 Hodgkin's lymphoma, lymphocyte depletion

#### ICD-10CM CODES

- C81.90 Hodgkin lymphoma, unspecified, unspecified site
- C81.00 Nodular lymphocyte predominant Hodgkin lymphoma, unspecified site
- C81.10 Nodular sclerosis classical Hodgkin lymphoma, unspecified site
- C81.20 Mixed cellularity classical Hodgkin lymphoma, unspecified site
- C81.30 Lymphocyte depleted classical Hodgkin lymphoma, unspecified site

### EPIDEMIOLOGY & DEMOGRAPHICS

- There is a bimodal age distribution (15 to 34 yr and >50 yr).
- Incidence is 4 in 100,000 cases.
- Concordance for Hodgkin's lymphoma in identical twins suggests that a genetic susceptibility underlies Hodgkin's lymphoma in young adulthood.
- There is association between certain HLA haplotypes, especially HLA-A1.
- The disease is more common in males (in childhood Hodgkin's lymphoma, >80% occur in males), whites, and higher socioeconomic groups.
- More common in people living in moderate climates.
- There are >8000 new cases of Hodgkin's lymphoma diagnosed annually in the United States.

### PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Painless palpable lymphadenopathy is the most common presenting symptom.
- Most common site of involvement: neck region.
- Fever and night sweats: fever in a cyclical pattern (days or weeks of fever alternating with afebrile periods) is known as Pel-Epstein fever.
- Unexplained weight loss, generalized malaise.

- Persistent, nonproductive cough.
- Pain associated with alcohol ingestion often because of heavy eosinophil infiltration of the tumor sites is relatively uncommon.
- Generalized pruritus.
- Hepatosplenomegaly in disease below the diaphragm.
- Other: superior vena cava syndrome, spinal cord compression (rare), erythema nodosum, ichthyosis.

### ETIOLOGY

Unknown; evidence implicating Epstein-Barr virus remains controversial.

## Dx DIAGNOSIS

### DIFFERENTIAL DIAGNOSIS

- Non-Hodgkin's lymphoma.
- Sarcoidosis.
- Infections (e.g., cytomegalovirus, Epstein-Barr virus, toxoplasmosis, HIV, tuberculosis).
- Drug reaction.

### WORKUP

Diagnosis is confirmed by lymph node biopsy. The World Health Organization classifies Hodgkin's lymphoma into two groups: classic Hodgkin's lymphoma (92% to 97%) and nodular lymphocyte-predominant Hodgkin's lymphoma (3% to 8%). Classic Hodgkin's lymphoma has four main histologic subtypes based on the number of lymphocytes, Reed-Sternberg cells, and the presence of fibrous tissue:

1. Nodular sclerosis (60% to 80%) ([Fig. EH1-57](#)).
2. Mixed cellularity (15% to 30%) ([Fig. EH1-58](#)).
3. Lymphocyte predominance (2% to 7%).
4. Lymphocyte depletion (1% to 6%).

Nodular sclerosis occurs mainly in young adulthood, whereas the mixed cellularity type is more prevalent after age 50 yr.

Staging: [Table H1-25](#) describes the Cotswolds staging classification.

Proper staging requires the following:

- Detailed history (with documentation of "B symptoms" and physical examination).
- Excisional biopsy with histologic, immunophenotypic and immunohistochemical analysis.
- Laboratory evaluation (complete blood count, erythrocyte sedimentation rate, blood urea nitrogen, creatinine, alkaline phosphatase, liver function tests, albumin, lactate dehydrogenase, HIV tests, uric acid), immunophenotypic markers (see [Table H1-26](#)). Gene-expression profiling for tumor-associated macrophages is a new biomarker for risk stratification.
- Chest x-ray (posteroanterior and lateral).
- CT scan of chest, abdomen, pelvis, neck.
- Positron emission tomography scan (18-FDG PET scan).
- Bilateral bone marrow biopsy (selected patients).

[Box H1-8](#) summarizes recommended staging procedures for Hodgkin lymphoma.

## Rx TREATMENT

### ACUTE GENERAL Rx

The main therapeutic modalities are radiotherapy and chemotherapy; the indication for which one varies with pathologic stage and other factors. In general, chemotherapy plus involved-field radiotherapy can be used as standard treatment for Hodgkin's lymphoma in early stages with favorable prognostic features. In patients with unfavorable features, 4 courses of chemotherapy plus involved-field radiotherapy should be the standard treatment. Commonly used therapeutic modalities are:

- Stage I and II: radiation therapy alone (involved-field radiotherapy [35 Gy]) unless a large mediastinal mass is present (mediastinal to thoracic ratio  $\geq 1.3$ ); in the latter case, a combination of chemotherapy and radiation

**TABLE H1-25 Cotswolds Staging Classification for Hodgkin's Lymphoma**

Classification	Description
Stage I	Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer ring) or involvement of a single extralymphatic site (IE)
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm (hilar nodes, when involved on both sides, constitute stage II disease); localized contiguous involvement of only one extranodal organ or site and lymph node regions on the same side of the diaphragm (IIE). The number of anatomic regions involved should be indicated by a subscript (e.g., II <sub>3</sub> )
III <sub>1</sub>	With or without involvement of splenic, hilar, celiac, or portal nodes
III <sub>2</sub>	With involvement of paraaortic, iliac, and mesenteric nodes
Stage IV	Diffuse or disseminated involvement of one or more extranodal organs or tissues, with or without associated lymph node involvement
A	Designations applicable to any disease stage
B	No symptoms
B	Fever (temperature, $>38^\circ\text{C}$ [ $100.4^\circ\text{F}$ ]), drenching night sweats, unexplained loss of $>10\%$ of body weight within the preceding 6 mo
X	Bulky disease (a widening of the mediastinum by more than one third of the presence of a nodal mass with a maximal dimension $<10\text{ cm}$ )
E	Involvement of a single extranodal site that is contiguous or proximal to the known nodal site

From Hoffman R et al: *Hematology: basic principles and practice*, ed 5, Philadelphia, 2009, Churchill Livingstone.

**TABLE H1-26** Selected Immunophenotypic Markers and Histologic Characteristics of Use in the Differential Diagnosis of Hodgkin's Lymphoma and Other Lymphoid Neoplasms

Marker	Classical HL	Nodular Lymphocyte Predominant HL	TCRBCL	ALCL
CD30	+	—	—	+
CD15	+	—	—	—
CD20	-/+*	+	+	—
CD45	—	+	+	+/-
CD79a	—	+	+	—
ALK	—	—	—	+/-
EMA	—	+	+	+
Nodular growth protein	+/-†	+	—	—

+, >90% of cases positive; +/-, majority of cases positive; -/-, minority of cases positive; -, <10% of cases positive; ALCL, anaplastic large cell lymphoma; HL, Hodgkin's lymphoma; TCRBCL, T-cell rich B-cell lymphoma.

\*CD20 positivity in classical Hodgkin's lymphoma is quite heterogeneous, with a wide range in brightness of staining.

†In classical Hodgkin's lymphoma, a nodular growth pattern is confined to the nodular sclerosing subtype.

From Abeloff MD: *Clinical oncology*, ed 3, Philadelphia, 2004, Saunders.

**TABLE H1-27** Characteristics of the ABVD Regimen

Agents: doxorubicin, bleomycin, vinblastine, dacarbazine
All intravenous, total compliance
80% complete response rate
10% primary refractory disease
60%-65% overall disease-free survival
Most relapses occur within the first 4 yr; however, about 10% of all relapses occur beyond 5 yr
Major side effects are nausea, phlebitis, myelosuppression, less cumulative myelotoxicity than MOPP
No infertility
No leukemia

ABVD, Adriamycin (doxorubicin), bleomycin, vinblastine, dacarbazine; MOPP, mechlorethamine, Oncovin (vincristine), procarbazine, prednisone.

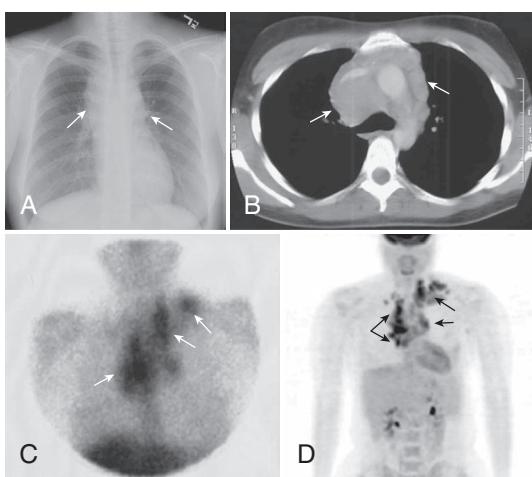
From Abeloff MD: *Clinical oncology*, ed 3, Philadelphia, 2004, Saunders.

#### BOX H1-8 Recommended Staging Procedures for Hodgkin Lymphoma

The following staging procedures are recommended for the initial workup of Hodgkin lymphoma:

1. Adequate surgical biopsy reviewed by an experienced hematopathologist
2. Core-needle biopsy of bone marrow from the posterior iliac crest; needle or surgical biopsy of any suspicious extranodal (e.g., hepatic, osseous, pulmonary, cutaneous) lesions; and cytologic examination of any effusion
3. Detailed history, with attention to the presence or absence of systemic symptoms, and a careful physical examination, emphasizing node chains, size of the liver and spleen, and inspection of Waldeyer ring
4. Routine laboratory tests: complete blood cell count, erythrocyte sedimentation rate, and liver function tests
5. Chest radiographs (posteroanterior and lateral) with measurement of the mass-to-thoracic ratio
6. Neck, chest, and abdominal CT
7. 18-FDG PET scan (Fig. H1-59)

From Hoffman R.; et al. *Hematology: basic principles and practice*, ed 5, Philadelphia, 2009, Churchill Livingstone.



**FIGURE H1-59** Imaging of Hodgkin's lymphoma. Bulky Hodgkin's disease as seen on chest radiograph (A), computed tomography (CT) of the chest (B), gallium scan (C), and positron emission tomography (PET) (D). The arrows indicate sites of disease. Note that the PET and CT scans provide more detailed information than the chest radiograph and gallium scan. (From Goldman L; Schafer Al. *Goldman's Cecil medicine*, ed 24, Philadelphia, 2012, Saunders.)

therapy is indicated. Various regimens can be used for combination of chemotherapy. Most oncologists prefer the combination of Adriamycin (doxorubicin), bleomycin, vinblastine, and dacarbazine (ABVD). Table H1-27 describes characteristics of the ABVD regimen. Generally, chemotherapy plus radiation treatment is effective in controlling stage IA or IIA nonbulky lymphoma in a high percentage of patients (>85%), but is associated with late treatment-related deaths. Trials have shown that ABVD therapy alone is associated with a higher rate of overall survival (due to lower rate of death from other causes) when compared with treatment that includes ABVD therapy and subtotal nodal radiation therapy.

- Stage IB or IIB: total nodal irradiation is often used, although chemotherapy is performed in many centers.
- Stage IIIA: treatment is controversial. It varies with the anatomic substage after splenectomy.
  1. III<sub>1</sub>A and minimum splenic involvement: radiation therapy alone may be adequate.
  2. III<sub>2</sub> or III<sub>1</sub>A with extensive splenic involvement: there is disagreement whether chemotherapy alone or a combination of chemotherapy and radiation therapy is the preferred treatment modality.
  3. IIIB and IVB: the treatment of choice is chemotherapy with or without adjuvant radiotherapy.

Recent trials have shown that in patients with early-stage Hodgkin's lymphoma and favorable prognosis, treatment with two cycles of ABVD followed by 20 Gy of involved-field radiation therapy may be as effective as, and less toxic than, four cycles of ABVD followed by 30 Gy of involved-field radiation therapy. Long-term effects of this approach need to be fully assessed before it becomes standard of care. BEACOPP, an intensified regimen consisting of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone, has been advocated by some as the new standard for treatment of advanced Hodgkin's

**TABLE H1-28** Definition of Treatment Groups According to the EORTC/GELA and GHSG

Treatment Group	EORTC/GELA	GHSG	NCIC/ECOG
Early-stage favorable	CS I-II without risk factors (supradiaphragmatic)	CS I-II without risk factors	Standard risk group: favorable CS I-II (without risk factors)
Early-stage unfavorable (intermediate)	CS I-II with $\geq 1$ risk factors (supradiaphragmatic)	CS I, CSIIA $\geq 1$ risk factors; CS IIB with C/D but without A/B	Standard risk group: unfavorable CS I-II (at least one risk factor)
Advanced stage	CS III-IV	CS IIB with A/B; CS III-IV	High-risk group: CS I or II with bulky disease; intraabdominal disease; CS III, IV
Risk factors (RF)	A large mediastinal mass B age $\geq 50$ yr C elevated ESR* D $\geq 4$ involved regions	A large mediastinal mass B extranodal disease C elevated ESR* D $\geq 3$ involved areas	A $\geq 40$ years B not NLPHL or NS histology C ESR $\geq 50$ mm/h D $\geq 4$ involved nodal regions

CS, Clinical stage; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; GELA, Groupe d'Etude des Lymphomes de l'Adulte; GHSG, German Hodgkin Study Group; NCIC, National Cancer Institute of Canada.

\*Erythrocyte sedimentation rate ( $\geq 50$  mm/h without or  $\geq 30$  mm/h with B-symptoms).

From Hoffman R et al: *Hematology, basic principles and practice*, ed 5, New York, 2009, Churchill Livingstone.

**TABLE H1-29** Recommendations for the Primary Treatment of Hodgkin's Lymphoma Outside of Clinical Trials

Group	Stage	Recommendation
Early stages (favorable)	CS I-II A/B, no RFs	2 cycles ABVD; 6 cycles EBVP; or VBM $\pm$ IF RT (20-30 Gy)
	Early stages (unfavorable, intermediate)	4-6 cycles ABVD; BEACOPP-baseline, Stanford V; or MOPP/ABV $\pm$ IF RT, 20-30 Gy
Advanced stages	CS I-II A/B + RFs	
	CS III A/B,	6-8 cycles ABVD; MOPP/ABV; ChlVPP/EVA; BEACOPP-escalated or BEACOPP-14 $\pm$ RT, 20-30 Gy for residual tumor (PET positive) and/or bulk disease
	CS IV A/B	

ABVD regimen, Adriamycin (doxorubicin), vinblastine, bleomycin, and dacarbazine; BEACOPP-baseline regimen, bleomycin, etoposide, Adriamycin (doxorubicin), cyclophosphamide, Oncovin (vincristine), procarbazine, and prednisone; BEACOPP-escalated regimen, bleomycin, etoposide, Adriamycin (doxorubicin), cyclophosphamide, Oncovin (vincristine), procarbazine, prednisone, and G-CSF; BEACOPP-14 regimen, bleomycin, etoposide, Adriamycin (doxorubicin), cyclophosphamide, Oncovin (vincristine), procarbazine, prednisone, and G-CSF; ChlVPP/EVA regimen, chlorambucil, vinblastine, procarbazine, prednisolone, etoposide, vincristine, Adriamycin (doxorubicin); CS, clinical stage; EBVP regimen, epirubicin, bleomycin, vinblastine, and prednisone; IF, involved field; MOPP regimen, mechlorethamine, Oncovin (vincristine), procarbazine, and prednisone; PET, positron emission tomography; RF, risk factors; RT, radiation therapy; Stanford V regimen, nitrogen mustard, doxorubicin, vinblastine, bleomycin, vincristine, etoposide, and prednisone; VBM regimen, vinblastine, bleomycin, and methotrexate.

From Hoffman R et al: *Hematology, basic principles and practice*, ed 5, New York, 2009, Churchill Livingstone.

lymphoma in place of ABVD. Recent trials have shown that treatment with BEACOPP, as compared with ABVD, resulted in better initial tumor control, but the long-term clinical outcome did not differ significantly between the two regimens. In addition, with the use of the escalated BEACOPP regimen, the rate of complications is higher (3% treatment-related death, 20% rate of hospitalization, and 3% rate of secondary leukemia). Thus, if the goal is cure with the least overall toxic effects, especially in elderly population, it is best to favor ABVD therapy, reserving rescue therapy with high-dose chemotherapy and autologous hematopoietic stem-cell transplantation for patients in whom the primary treatment fails. Stanford V (vinblastine, doxorubicin, mechlorethamine, bleomycin, etoposide, vincristine, and prednisone) may be preferred in some cases due to its short administration schedule combining radiation.

- Definitions of treatment groups are described in Table H1-28.
- Recommendations for the primary treatment of Hodgkin's lymphoma outside of clinical trials are described in Table H1-29.

## DISPOSITION

- The overall survival at 10 yr is ~60%.
- Cure rates as high as 75% to 80% are now possible with appropriate initial therapy.
- Polyvalent pneumococcal vaccine and other vaccines should be administered especially in patients undergoing splenectomy.
- Poor prognostic features (Table H1-30) include presence of B symptoms, advanced age, advanced stage at initial presentation, mixed cellularity and lymphocyte depletion histology, and increased number of tumor-associated macrophages.
- Chemotherapy significantly increases the risk of leukemia.
- The peak in risk of leukemia is seen approximately 5 yr after the initiation of chemotherapy.
- The risk of leukemia is greater for those who undergo splenectomy and patients with advanced stages of Hodgkin's disease; the risk is unaffected by concomitant radiotherapy.
- Involved-field radiotherapy does not improve the outcome in patients with advanced-stage

**TABLE H1-30** Prognostic Factors of Importance in Advanced Hodgkin's Lymphoma\*

Gender	Male
Age	>45 yr
Stage	IV
Hemoglobin	<105 g/L
White blood cell count	$>15 \times 10^9/L$
Lymphocyte count	$<0.6 \times 10^9/L$ or <8% of the white cell differential
Serum albumin	<40 g/L

\*Identified by the International Prognostic Factors Project on Advanced Hodgkin's Disease.

From Abeloff MD: *Clinical oncology*, ed 3, Philadelphia, 2004, Saunders.

Hodgkin's lymphoma who have a complete remission after MOPP (mechlorethamine, vincristine, procarbazine, and prednisone)—ABV chemotherapy. Radiotherapy may benefit patients with a partial response after chemotherapy.

- Mediastinal irradiation increases the risk of subsequent death from heart disease caused by sclerosis of the coronary artery from irradiation. Risk increases with high mediastinal doses, minimal protective cardiac blocking, young age at irradiation, and increased duration of follow-up.
- Both chemotherapy and radiation therapy increase the risk of developing secondary solid tumors (Table H1-31).
- Table H1-32 describes potential late complications of Hodgkin's lymphoma treatment and appropriate clinical responses and preventive strategies.

## REFERRAL

- To surgery for lymph node biopsy.
- Hematology/oncology.

**TABLE H1-31** Second Neoplasms Seen with Increased Frequency After Successful Hodgkin's Lymphoma Treatment

Acute myelogenous leukemia/myelodysplasia
Non-Hodgkin's lymphoma
Melanoma
Soft tissue sarcoma
Adenocarcinoma
Breast
Thyroid
Lung
Stomach and esophagus
Squamous cell carcinoma
Skin
Uterine cervix
Head and neck

From Abeloff MD: *Clinical oncology*, ed 3, Philadelphia, 2004, Saunders.

## PEARLS & CONSIDERATIONS

### COMMENTS

- Young male patients should consider sperm banking before the initiation of therapy.
- Chemotherapy plus involved-field radiotherapy should be the standard treatment for Hodgkin's disease with favorable prognostic features. In patients with unfavorable features, 4 courses of chemotherapy plus involved-field radiotherapy should be the standard of treatment. After failure of ABVD therapy, more than 60% of patients who have had a relapse and about 30% of patients with initially refractory lymphoma can be reliably cured with high-dose chemotherapy and autologous hematopoietic stem-cell transplantation.

- Preclinical studies suggest that Reed-Sternberg cells exploit the programmed death 1 (PD-1) pathway to evade immune detection. Phase 1 trials with nivolumab, a PD-1 blocking antibody, have shown substantial therapeutic activity and an acceptable safety profile in patients with previously treated relapsed or refractory Hodgkin's lymphoma.<sup>1</sup>

### SUGGESTED READINGS

Available at [www.expertconsult.com](http://www.expertconsult.com)

### RELATED CONTENT

Hodgkin's Lymphoma (Patient Information)

AUTHORS: SYEDA M. SAYEED, M.D., and FRED F. FERRI, M.D.

<sup>1</sup>Ansell SM et al.: PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma, *N Engl J Med* 372:311-319, 2015.

**TABLE H1-32** Potential Late Complications of Hodgkin's Lymphoma Treatment and Appropriate Clinical Responses and Preventive Strategies

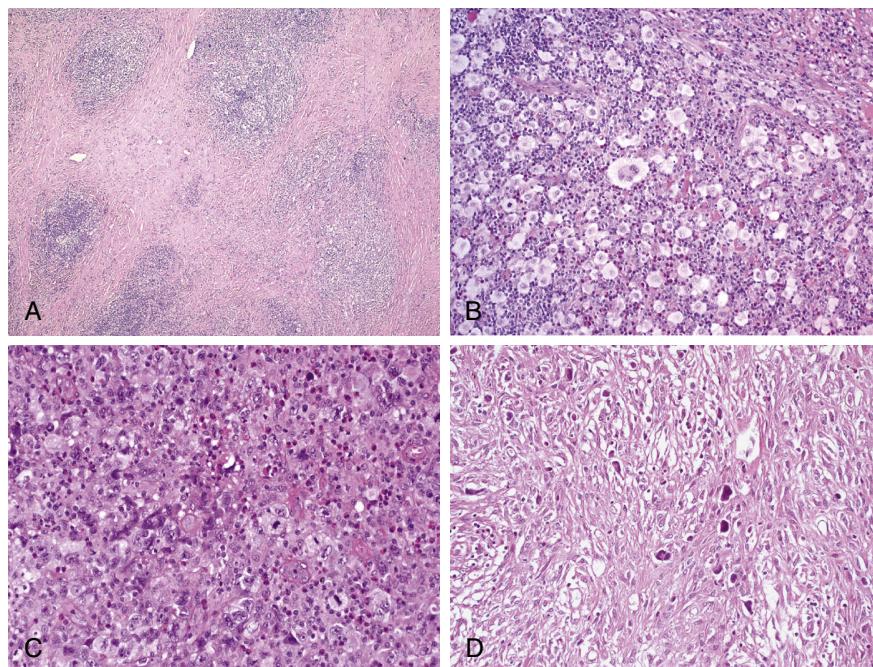
Risk/Problem	Incidence/Response
Dental caries	Neck or oropharyngeal irradiation can cause decreased salivation. Patients should have careful dental care follow-up and should make their dentist aware of the previous irradiation.
Hypothyroidism	After external beam irradiation that encompasses the thyroid with doses sufficient to cure Hodgkin's lymphoma, at least 50% of patients will eventually become hypothyroid. All patients whose TSH level becomes elevated should be treated with lifelong thyroxine replacement in doses sufficient to suppress TSH levels to low normal. This is also necessary to ensure that the radiation-damaged thyroid is not subjected to long-term stimulation by thyroid-stimulating hormone, which can increase the risk of thyroid neoplasm.
Infertility	ABVD is not known to cause any permanent gonadal toxicity, although oligospermia for 1-2 yr after treatment is common. Direct or scatter radiation to gonadal tissue can cause infertility, amenorrhea, or premature menopause, but this seldom occurs with the current fields used for the treatment of Hodgkin's lymphoma. Thus, with the current chemotherapy regimens and radiation fields used, most patients will not develop these problems. In general, after treatment, women who continue menstruating are fertile, but men require semen analysis to provide a specific answer. High-dose chemoradiotherapy and hematopoietic stem cell transplantation almost always cause permanent infertility in both genders, although some young women occasionally recover fertility.
Impaired immunity to infections	Hodgkin's lymphoma and its treatment can lead to lifelong impairment of full immunity to infection. All patients should be given annual influenza immunization and pneumococcal immunization every 5 years. Patients whose spleen has been irradiated or removed should also be immunized against meningococcal types A and C and <i>Haemophilus influenza</i> type B. As for all adults, diphtheria and tetanus immunizations should be kept up-to-date.
Secondary neoplasms	Although uncommon, certain secondary neoplasms occur with increased frequency in patients who have been treated for Hodgkin's lymphoma. These include acute myelogenous leukemia, thyroid, breast, lung, and upper gastrointestinal carcinoma and melanoma, and cervical carcinoma in situ. It is appropriate to screen for these neoplasms for the rest of the patient's life because they might have lengthy induction periods.

ABVD, Adriamycin, bleomycin, vinblastine, dacarbazine; TSH, thyroid-stimulating hormone.

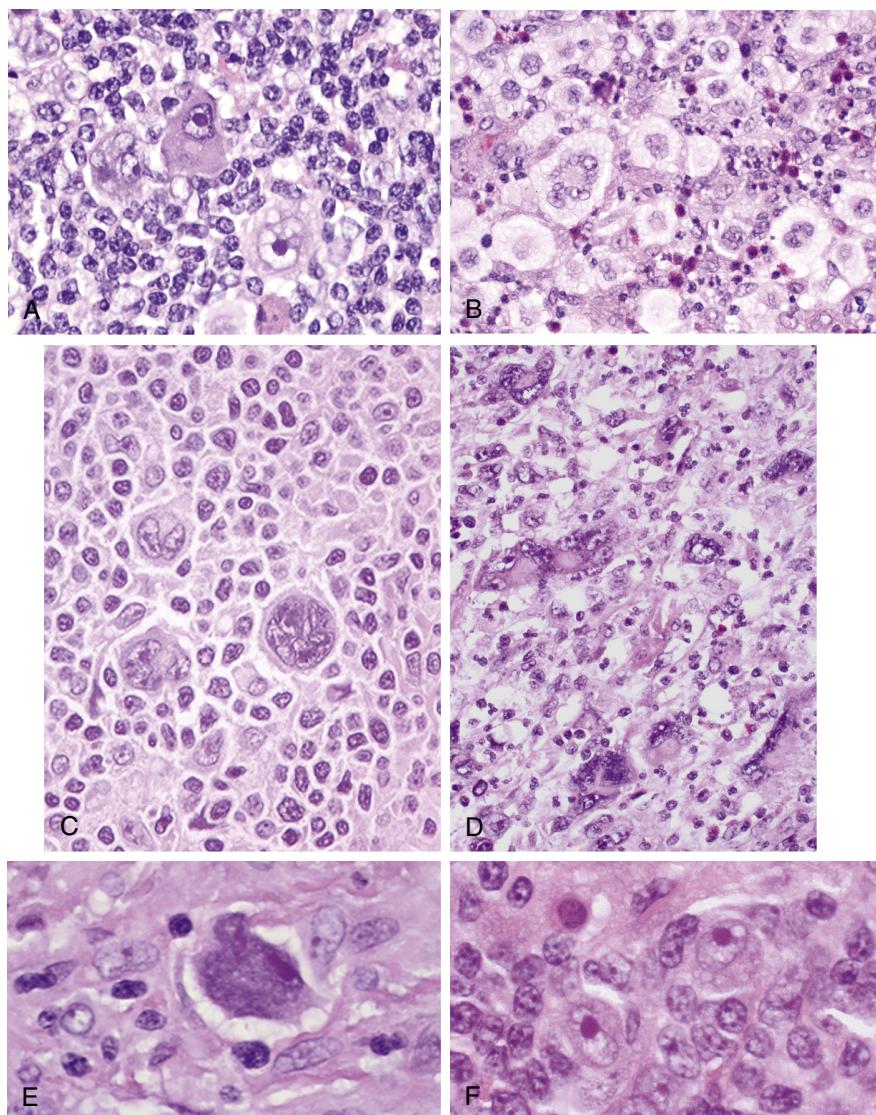
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**FIGURE EH1-57 Hodgkin's lymphoma.** Morphology of classical Hodgkin's lymphoma (CHL). **A**, Nodular sclerosis CHL. Cellular nodules are separated by concentric bands of mature collagen. **B**, Close-up of cellular nodule shows numerous lacunar cells with clear cytoplasm intermingled with lymphocytes, neutrophils, and eosinophils. Note collagen bands rimming the nodule. **C**, Nodular sclerosis CHL grade II. Confluent sheets of neoplastic cells with partly anaplastic features intermingled with a minority of inflammatory cells. This morphology is consistent with the so-called syncytial variant of CHL. **D**, Lymphocyte-depleted CHL, diffuse fibrosis subtype. Neoplastic Reed-Sternberg and Hodgkin cells in a hypocellular background with histiocytes and fibroblasts. This case lacks nodularity and ordered collagen bands. (From Jaffe ES et al: *Hematopathology*, Philadelphia, 2011, Saunders.)



**FIGURE EH1-58 Hodgkin's lymphoma.** Cytologic features of Reed-Sternberg (RS) cells and Hodgkin cells. **A**, Classic RS cells and variants in mixed cellularity—classic Hodgkin's lymphoma (CHL), with amphophilic cytoplasm, large nuclei with clear karyoplasm, and huge viral inclusion-like nucleoli. **B**, Typical lacunar cells in a case of nodular sclerosis CHL. Note the delicate folded nuclear membranes, less conspicuous nucleoli, and ample clear cytoplasm with threadlike protrusions. **C**, Typical RS cells, including a binuclear variant, in mixed cellularity CHL. **D**, Abundant, sometimes bizarre multinucleated tumor cells in a case of nodular sclerosis grade II. **E**, So-called mummified RS cell with condensed, deeply basophilic cytoplasm. **F**, Two classic mononuclear Hodgkin cells in a case of mixed cellularity CHL. (From Jaffe ES et al: *Hematopathology*, Philadelphia, 2011, Saunders.)



## BASIC INFORMATION

### DEFINITION

Hookworm is a parasitic infection of the intestine caused by the soil helminths *Necator americanus* and *Ancylostoma duodenale*.

### SYNOMYS

Ground itch

*Ancylostoma duodenale* infection

*Necator americanus* infection

### ICD-9CM CODES

126.35 Hookworm

### ICD-10CM CODES

B76.9 Hookworm disease, unspecified

## EPIDEMIOLOGY & DEMOGRAPHICS

### INCIDENCE (IN U.S.)

- Varies greatly in different areas of the United States.
- Most common in rural areas of southeastern United States.
- Poor sanitation and increased rainfall increase incidence.

**PREVALENCE (IN U.S.):** Varies from 10% to 90% in regions where it is found.

**PREDOMINANT AGE:** Schoolchildren.

## PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Nonspecific abdominal complaints.
- Symptoms related to iron deficiency anemia depending on the amount of iron in the diet and worm burden (these organisms consume host's RBCs).
- Fatigue, tachycardia, dyspnea, and high-output failure.
- Hypoproteinemia and edema from loss of proteins into the intestinal tract.
- Unusual for pulmonary manifestations to occur when the larvae migrate through the lungs.
- Skin rash at sites of larval penetration in some individuals without prior exposure: ground itch.

### ETIOLOGY

Two species can cause this disease: *N. americanus* and *A. duodenale*. *N. americanus* is the pre-

dominant cause of hookworm in the United States. They are soil nematodes (geohelminthic infections) that are acquired by skin contact (i.e., bare feet) with contaminated soils in moist, warm climate. Worldwide, over 700 million people are infected.

- Infection occurs via penetration of the skin by the larval form, with subsequent migration via the bloodstream to the alveoli, up the respiratory tract, then into the GI tract (Fig. H1-60).
- Ancylostoma* spp. infection can also occur via the oral route through ingestion of contaminated water supplies.
- Sharp mouth parts allow for attachment to intestinal mucosa.
- Ancylostoma* spp. are more likely to cause iron deficiency anemia because they are larger and remove more blood daily from the bowel wall than the other hookworm species, *N. americanus*.

## Dx DIAGNOSIS

### DIFFERENTIAL DIAGNOSIS

- Strongyloidiasis.
- Ascariasis.
- Other causes of iron deficiency anemia and malabsorption.

### WORKUP

Examine stool for hookworm eggs. Shedding of eggs starts around 8 weeks after skin penetration in *N. americanum* infections and longer with *A. duodenale*, but eggs are indistinguishable between the two species.

### LABORATORY TESTS

CBC to show hypochromic, microcytic anemia; possible mild eosinophilia and hypoalbuminemia.

### IMAGING STUDIES

Chest x-ray: generally not helpful, occasionally shows opacities.

## Rx TREATMENT

### NONPHARMACOLOGIC THERAPY

- Prevention of disease by not walking barefoot and by improving sanitary conditions.
- Vaccines are in development.

**FIGURE H1-60 Life cycle of intestinal nematodes with a migratory phase through the lungs.** Eggs are passed with stools in *Ascaris lumbricoides* (A.I.), *Necator americanus*, or *Ancylostoma duodenale* (A.d.), or they hatch on their way out in *Strongyloides stercoralis* (S.s.). Ascaris eggs mature in soil, and humans are infected upon ingestion of these eggs. With hookworm and strongyloidiasis, humans are infected via skin penetration by filariform larvae. In all three infections, larvae pass through a migratory phase via the lungs before reaching maturity at their final habitat in the small intestine. (From Mandell GL et al: *Principles and practice of infectious diseases*, ed 7, Philadelphia, 2010, Churchill Livingstone.)

### ACUTE GENERAL Rx

- Albendazole 400 mg once PO has become preferred treatment.
- Mebendazole 100 mg PO bid for 3 days or as a 500-mg single dose.
- Pyrantel pamoate 11 mg/kg (to max dose of 1 g) PO qd × 3 days.
- Iron supplementation may be helpful in patients with iron deficiency.

### DISPOSITION

Easily treated.

### REFERRAL

To gastroenterologist and infectious disease specialist if diagnosis uncertain.

## PEARLS & CONSIDERATIONS

### COMMENTS

- Appropriate disposal of human wastes is important in controlling the disease in areas with a high prevalence of hookworm infestation.
- Wearing shoes will avoid contact with contaminated soils, and the provision of safe water and sanitation for disposing human excreta is important in control of hookworm.

## EBM EVIDENCE

Available at [www.expertconsult.com](http://www.expertconsult.com)

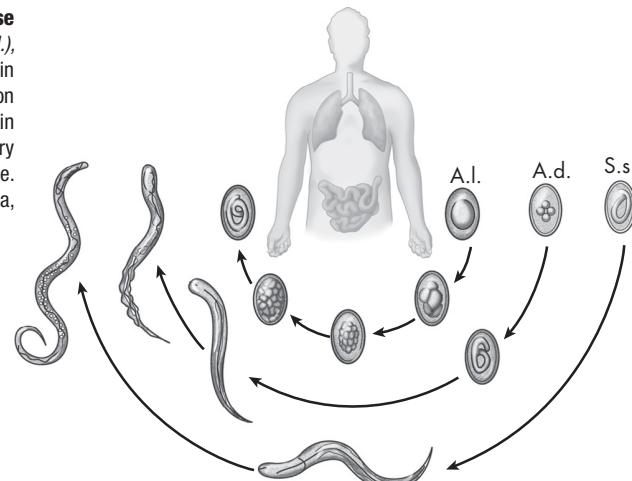
## SUGGESTED READINGS

Available at [www.expertconsult.com](http://www.expertconsult.com)

### RELATED CONTENT

Hookworm Infection (Patient Information)

AUTHOR: GLENN G. FORT, M.D., M.P.H.





## EBM EVIDENCE

### Abstract<sup>[1]</sup>

#### Background and Aims:

The association between hygiene and prevalence of autoimmune disease has been attributed in part to enteric helminth infection. A pilot study of experimental infection with the hookworm *Necator americanus* was undertaken among a group of otherwise healthy people with celiac disease to test the potential of the helminth to suppress the immunopathology induced by gluten.

#### Methods:

In a 21 week, double-blinded, placebo-controlled study, we explored the effects of *N. americanus* infection in 20 healthy, helminth-naïve adults with celiac disease well controlled by diet. Staged cutaneous inoculations with 10 and 5 infective 3<sup>rd</sup> stage hookworm larvae or placebo were performed at week –0 and –12 respectively. At week –20, a five day oral wheat challenge equivalent to 16 grams of gluten per day was undertaken. Primary outcomes included duodenal Marsh score and quantification of the immunodominant  $\alpha$ -gliadin peptide (QE65)-specific systemic interferon- $\gamma$ -producing cells by ELISpot pre- and post-wheat challenge.

#### Results:

Enteric colonisation with hookworm established in all 10 cases, resulting in transiently painful enteritis in 5. Chronic infection was asymptomatic, with no effect on hemoglobin levels. Although some duodenal eosinophilia was apparent, hookworm-infected mucosa retained a healthy appearance. In both groups, wheat challenge caused deterioration in both primary and several secondary outcomes.

#### Conclusions:

Experimental *N. americanus* infection proved to be safe and enabled testing its effect on a range of measures of the human autoimmune response. Infection imposed no obvious benefit on pathology. **A**

### Evidence-Based Reference

Daveson AJ et al.: Effect of hookworm infection on wheat challenge in celiac disease—a randomised double-blinded placebo controlled trial, *PLoS One* 6:e17366, 2011. **A**

### SUGGESTED READINGS

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## BASIC INFORMATION

### DEFINITION

A hordeolum is an acute inflammatory process affecting the eyelid and arising from the meibomian (posterior) or Zeis (anterior) glands. It is most often infectious and usually caused by *Staphylococcus aureus*. When infection involves the meibomian glands, it is called meibomianitis.

### SYNOMYS

Stye  
Meibomianitis

#### ICD-9CM CODES

373.11 External hordeolum  
373.12 Internal hordeolum

#### ICD-10CM CODES

H00.019 Hordeolum externum unspecified eye, unspecified eyelid  
H00.029 Hordeolum internum unspecified eye, unspecified eyelid

### EPIDEMIOLOGY & DEMOGRAPHICS

**INCIDENCE (IN U.S.):** Unknown.

**PREVALENCE (IN U.S.):** Unknown.

**PREDOMINANT SEX:** No gender predilection.

**PREDOMINANT AGE:** May occur at any age.

**NEONATAL INFECTION:** Rare in the neonatal period.

**PEAK INCIDENCE:** May occur at any age.



**FIGURE H1-61 External stye.** (From Palay D [ed]: *Ophthalmology for the primary care physician*, St Louis, 1997, Mosby.)

### PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Abrupt onset with pain and erythema of the eyelid.
- Localized, tender mass in the eyelid (Fig. H1-61).
- May be associated with blepharitis.
- External hordeolum: points toward the skin surface of the lid and may spontaneously drain.
- Internal hordeolum: can point toward the conjunctival side of the lid and may cause conjunctival inflammation.

### ETIOLOGY

- 75% to 95% of cases are caused by *S. aureus*.
- Occasional cases are caused by *Streptococcus pneumoniae*, other streptococci, gram-negative enteric organisms, or mixed bacterial flora.

## Dx DIAGNOSIS

### DIFFERENTIAL DIAGNOSIS

- Eyelid abscess.
- Chalazion.
- Allergy or contact dermatitis with conjunctival edema.
- Acute dacryocystitis.
- Herpes simplex infection.
- Cellulitis of the eyelid.

### LABORATORY TESTS

- Generally, none are necessary.
- If incision and drainage are performed, specimens should be sent for bacterial culture.

## Rx TREATMENT

### NONPHARMACOLOGIC THERAPY

External stye (eyelash follicle): Usually responds to warm compresses and will drain spontaneously

### ACUTE GENERAL Rx

- Systemic antibiotics generally not necessary.
- For internal stye, use hot packs plus oral dicloxacillin 500 mg qid x 7 days. If suspecting MRSA, use trimethoprim-sulfamethoxazole DS bid in place of dicloxacillin. In patients with hospital-acquired infection, consider linezolid 600 mg PO bid.
- For external stye, topical erythromycin ophthalmic ointment applied to the lid margins two to four times daily until resolution may be helpful in some cases.
- Incision and drainage: rarely needed but should be considered for progressive infections.

### DISPOSITION

- Usually sporadic occurrence.
- Possible relapse if resolution is not complete.

### REFERRAL

- For evaluation by an ophthalmologist if visual acuity or ocular movement is affected or if the diagnosis is in doubt.
- For surgical drainage if necessary.

## PEARLS & CONSIDERATIONS

### COMMENTS

Seborrheic dermatitis may coexist with hordeolum.

### SUGGESTED READINGS

Available at [www.expertconsult.com](http://www.expertconsult.com)

### RELATED CONTENT

Stye (Hordeolum) (Patient Information)

AUTHOR: GLENN G. FORT, M.D., M.P.H.

## SUGGESTED READINGS

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- Kiratli HK, Akar Y: Multiple recurrent hordeola associated with selective IgM deficiency, *JAPOS* 5(1):60, 2001.
- Lindsley K et al.: Interventions for acute internal hordeolum, *Cochrane Database Syst Rev* 9:CD007742, 2010.



## BASIC INFORMATION

### DEFINITION

Horner's syndrome is the clinical triad of ipsilateral ptosis, miosis, and sometimes facial anhidrosis. Disruption of any of the three neurons in the oculosympathetic pathway (first-order, second-order, or third-order) can cause Horner's syndrome.

### SYNOMYS

Oculosympathetic paresis

Raeder's paratrigeminal syndrome: Horner's syndrome of the third-order neuron associated with pain in the trigeminal nerve distribution

#### ICD-9CM CODES

337.9 Horner's syndrome

#### ICD-10CM CODES

G90.2 Horner's Syndrome

### EPIDEMIOLOGY & DEMOGRAPHICS

Congenital or acquired.

### PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Ptosis is usually mild. It results from loss of sympathetic tone to Müller's muscle, which contributes approximately 2 mm of upper eyelid elevation. Weakness of the corresponding muscle in the lower eyelid causes it to elevate slightly. This combination causes narrowing of the palpebral fissure. Levator function of the eyelid is preserved.
- Miosis results from loss of sympathetic innervation to the iris dilator muscle (Fig. H1-62). The affected pupil reacts normally to bright light and accommodation. Anisocoria is greater in dim light.
  1. Dilation lag: Horner's pupil dilates more slowly than the normal pupil when lights are dimmed (20 versus 5 sec) because it dilates passively as a result of relaxation of the iris sphincter.
- Presence of facial anhidrosis is variable and depends on the site of injury. It occurs with lesions affecting first-order or second-order neurons.
- Congenital Horner's syndrome may result in heterochromia. The affected eye has a lighter-colored iris.
- Acute cases may also present with conjunctival injection from the loss of sympathetic vasoconstriction.



**FIGURE H1-62 Horner's syndrome.** The mild ptosis (1 to 2 mm) and the smaller pupil (in room light) can be seen on the affected right side. (From Palay D [ed]: *Ophthalmology for the primary care physician*, St Louis, 1997, Mosby.)

### ETIOLOGY

Disruption of the ipsilateral sympathetic innervation to the eye and face. Lesions can damage any of the three neurons in the oculosympathetic pathway (Fig. EH1-63). First order neuron lesions are least common but are usually caused by pathology in the hypothalamus, brainstem, or cervical spinal cord. Second order neuron lesions are often caused by disease involving the cervicothoracic spinal cord, lung apex, or anterior neck. Third order neuron lesions are usually seen with disease in the internal carotid artery, skull base, cavernous sinus, or orbital apex. Location is often suggested by the presence of associated findings. Vascular disease and neoplasm must be considered.

Mechanical:

- Syringomyelia.
- Trauma.
- Tumors: benign, malignant head and neck cancers (thyroid, apical lung, mediastinal).
- Lymphadenopathy.
- Neurofibromatosis.
- Cervical rib.

Vascular (ischemia, hemorrhage or arteriovenous malformation):

- Brainstem lesion: commonly occlusion of the posterior inferior cerebellar artery but other arteries may be responsible (vertebral; superior, middle or inferior lateral medullary arteries; superior or anterior inferior cerebellar arteries).
- Carotid artery aneurysm or dissection. Can also be from injury to other major vessels (internal carotid artery, subclavian artery, ascending aorta).
- Cavernous sinus thrombosis.
- Cluster headache, migraine.
- Miscellaneous:
- Idiopathic.
- Congenital.
- Demyelination (multiple sclerosis).
- Infection (apical tuberculosis, herpes zoster, Lyme disease).
- Myelitis.
- Pneumothorax.
- Iatrogenic (angiography, internal jugular/subclavian catheter, chest tube, neck or upper thoracic surgery, epidural spinal anesthesia).

### Dx DIAGNOSIS

#### DIFFERENTIAL DIAGNOSIS

Causes of anisocoria (unequal pupils):

- Normal variant.
- Mydriatic use.
- Prosthetic eye.
- Prior eye surgery.
- Unilateral cataract.
- Iritis.

Causes of ptosis are described in Section II.

#### WORKUP

History, physical examination, pharmacologic testing, imaging.

#### PHARMACOLOGIC TESTING

- Topical cocaine test: confirms sympathetic denervation (drops dilate normal pupil but not Horner's pupil).

- Topical apraclonidine test: confirms diagnosis (drops reverse anisocoria by causing dilation of Horner's pupil and constriction of normal pupil).

- Topical hydroxyamphetamine test: distinguishes first- and second-order neuron lesions from third-order sympathetic lesions (drops dilate normal pupil and first- or second-order Horner's pupil, but not third-order Horner's pupil). Testing must be delayed >48 hr after topical cocaine or apraclonidine testing.

### IMAGING STUDIES

Results of pharmacologic testing as well as accompanying signs and symptoms should guide imaging:

- MRI brain: brainstem (diplopia, vertigo, ataxia); cavernous sinus (eye movement abnormalities, sixth nerve palsy).
- MRI cervical and upper thoracic spinal cord: sensory changes/weakness of extremities, bowel/bladder dysfunction.
- MR or CT angiography (ultrasound is less sensitive): carotid artery dissection (acute Horner's syndrome with face or neck pain).
- CT chest and neck: evaluate lung apex, perivertebral areas, mediastinum if symptoms do not localize to the central nervous system; brachial plexus lesion (arm/hand pain or weakness).

### Rx TREATMENT

- Treatment depends on underlying cause.
- Ptosis can be surgically corrected or treated with medication (phenylephrine drops).

### REFERRAL

Ophthalmologist for pharmacologic testing to confirm diagnosis and localize lesion.

### PEARLS & CONSIDERATIONS

- May be the presentation of a life-threatening condition. Horner's syndrome presenting acutely or associated with pain, trauma, or history of malignancy should be evaluated urgently.
- Normal variant anisocoria:
  1. Occurs in 20% of people.
  2. Usually <1 mm difference between pupils.
  3. Pupils are round and display a normal, brisk constriction and dilation response to light.

### SUGGESTED READINGS

Available at [www.expertconsult.com](http://www.expertconsult.com)

### RELATED CONTENT

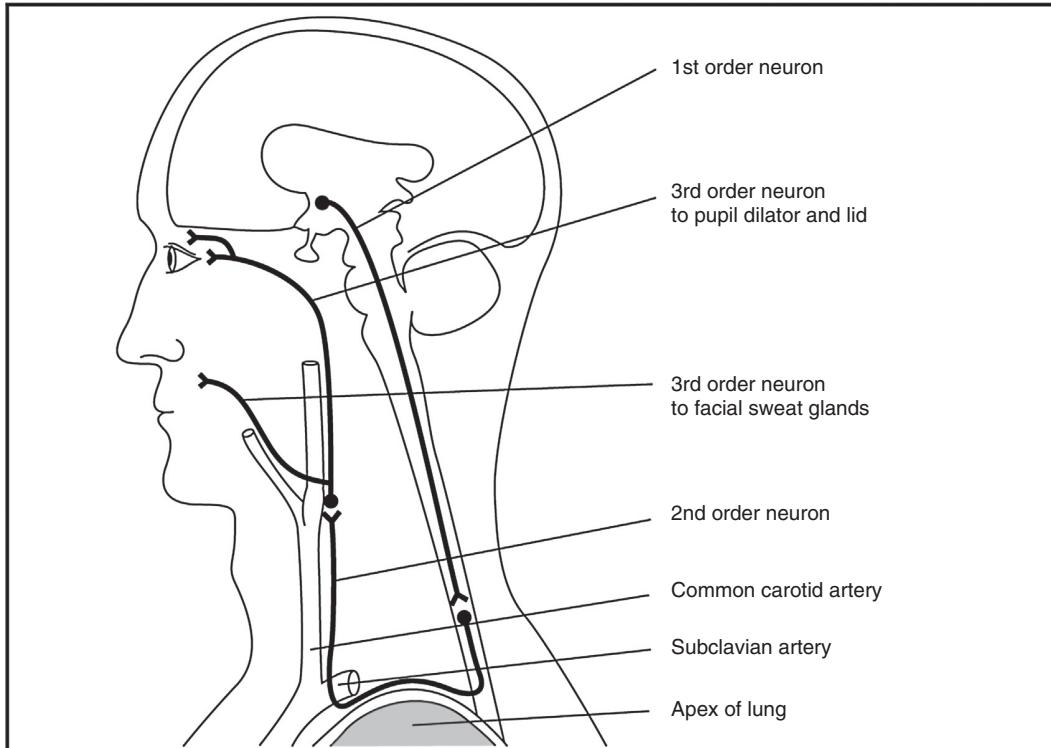
Horner's Syndrome (Patient Information)

Lung Neoplasms, Primary (Related Key Topic)

AUTHOR: SUDEEP KAUR AULAKH, M.D.

## SUGGESTED READINGS

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- Murphy MA et al.: Lyme disease associated with postganglionic Horner syndrome and Raeder par trigeminal neuralgia, *J Neuro-ophthalmol* 27(2):123, 2007.
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**FIGURE EH1-63 Anatomy of sympathetic pathways to the eye.** The sympathetic innervation of the eye consists of three neurons connected in series: first order neurons, second order neurons, and third order neurons. The first order neurons (central neurons) extend from the posterior hypothalamus to the C8 to T2 level of the spinal cord. The second order neurons (preganglionic neurons) leave the spinal cord and travel over the lung apex, around the subclavian artery, and along the carotid artery to the superior cervical ganglion. The third order neurons (postganglionic neurons) diverge and take two paths: Those to the pupil and lid muscles travel along the internal carotid artery through the cavernous sinus to reach the orbit; those to the facial sweat glands travel with the external carotid artery to the face. Lesions in any of these neurons cause Horner syndrome and distinct associated physical signs. (From McGee [ed]: *Evidence-based physical diagnosis*, 3rd ed. Philadelphia, 2012, Saunders.)



## BASIC INFORMATION

### DEFINITION

Hot flashes are sudden onset of intense warmth that begins in the neck or face, or in the chest and progresses to the neck and face; often associated with profuse sweating, anxiety, and palpitations.

### ICD-9CM CODES

627.2 Hot flashes

### ICD-10CM CODES

N95.1 Menopausal and female climacteric states

R23.2 Flushing

### EPIDEMIOLOGY & DEMOGRAPHICS

- Hot flashes affect 75% of postmenopausal women.
- Most hot flashes begin 1 to 2 yr before menopause and resolve after 2 yr.
- 15% of women report duration of hot flashes >15 yr.

### PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Profuse sweating and red blotching of skin may be noted during the vasomotor event.
- Palpitations and hyperreflexia may be present during the hot flash.
- Hot flashes typically last 1 to 5 min.
- Each hot flash is associated with increase in temperature, increased pulse rate, and increased blood flow into the hands and face.
- Hot flashes during sleep are common and are referred to as *night sweats*.
- There is considerable variation in the frequency of hot flashes. One third of women report more than 10 flashes per day.

### Etiology

- Dysfunction of central thermoregulatory centers caused by changes in estrogen level at the time of menopause.
- Tamoxifen use.
- Chemotherapy-induced ovarian failure.
- Androgen ablation therapy for prostate carcinoma.



## DIAGNOSIS

### DIFFERENTIAL DIAGNOSIS

- Carcinoid syndrome.
- Anxiety disorder.
- Idiopathic flushing.
- Lymphoma (night sweats).
- Hyperthyroidism.
- Hyperhidrosis.

### WORKUP

Evaluation of hot flashes is aimed at excluding the conditions listed in the differential diagnosis.

### LABORATORY TESTS

- Follicle-stimulating hormone (FSH), luteinizing hormone, estradiol level. The serum FSH levels rather than estradiol levels are associated with greater severity of hot flashes in older postmenopausal women, suggesting that nonestrogen feedback systems may be important in modulating the severity of hot flashes. It is not necessary to obtain an FSH to make the diagnosis of menopausal status, however. An amenorrheic woman over age 50 with vasomotor symptoms is assumed to have made the menopausal transition and serum markers of menopause are not required to complete the diagnosis.
- Thyroid-stimulating hormone (TSH).

## RX TREATMENT

### NONPHARMACOLOGIC THERAPY

- Behavioral interventions such as relaxation training and paced respiration have been reported effective in reducing symptoms in some women.
- Avoidance of caffeine, alcohol, tobacco, and spicy foods may be beneficial.

### GENERAL Rx

- Estrogen replacement therapy reduces hot flashes by 80% to 90%. Estrogen therapy, however, is contraindicated in many women, and others are fearful of its use. Potential risks and side effects should be considered before using estrogen in any patient. When using estrogen, it is best to use low dose (e.g., Prempro [conjugated equine estrogen 0.45 mg or 0.3 mg plus medroxyprogesterone 1.5 mg]). Femring is an intravaginal ring that is changed every 3 mo and approved to treat vasomotor symptoms in women who have had a hysterectomy. It provides both local and systemic estrogen.
- Megestrol acetate, a progestational agent, is a safer alternative to estrogen in women with a history of receptor-positive breast or uterine cancer and in men receiving androgen ablation therapy for prostate cancer. Usual dose is 20 mg bid.
- The antidepressant venlafaxine has been reported to be 60% effective in reducing hot flashes and represents an alternative treatment modality in women unable or unwilling to use estrogens. Starting dose is 37.5 mg qd, increased as tolerated up to a maximum of 300 mg/day. Other antidepressants such as desvenlafaxine and escitalopram have

also been shown to be effective in reducing the number and severity of menopausal hot flashes. A recent trial showed that paroxetine is also an effective agent for diminishing hot flashes in post-menopausal women and men receiving androgen ablation therapy.

- Duavée is a new FDA-approved treatment of moderate to severe vasomotor menopausal symptoms. It consists of a combination of conjugated estrogens and bazedoxifene, a new selective estrogen receptor modulator (SERM).
- The anticonvulsant gabapentin (300 to 1200 mg/day) represents another nonhormonal alternative in the treatment of hot flashes and can be used alone or in combination with venlafaxine.
- The antihypertensive clonidine is also somewhat effective in reducing the frequency of hot flashes in mild cases. Adverse effects include dry mouth, sedation, and dizziness.
- Vitamin E (800 IU/day) may be effective in patients with mild symptoms that do not interfere with sleep or daily function.
- Soy protein (use of soy extracts that contain plant-derived estrogens [phytoestrogens]) is often used; however, clinical trials have not shown clear efficacy.
- Several classes of herbal remedies are available to patients and are commonly used, generally without significant benefit. Frequently used agents are *Cimicifuga racemosa* (black cohosh, snakeroot, bugbane), *Angelica sinensis*, and evening primrose (evening star). Recent trials using the isopropanolic extract of black cohosh rootstock (Remefemin) did show some improvement in controlling menopausal symptoms. Such alternative medications may be used to treat mild to moderate symptoms, but it is possible that symptomatic improvements may derive in part from a placebo effect.

### SUGGESTED READINGS

Available at [www.expertconsult.com](http://www.expertconsult.com)

### RELATED CONTENT

Hot Flashes (Patient Information)

Menopause (Related Key Topic)

AUTHOR: FRED F. FERRI, M.D.

## SUGGESTED READINGS

- Archer DF et al.: A double-blind, randomly assigned, placebo-controlled study of desvenlafaxine efficacy and safety for the treatment of vasomotor symptoms associated with menopause, *Am J Obstet Gynecol* 200(2):172.e1–172.e10, 2008.
- Freeman EW et al.: Efficacy of escitalopram for hot flashes in healthy menopausal women, a randomized controlled trial, *JAMA* 305(3):267–274, 2011.
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- Sikon A, Thacker HL: Treatment options for menopausal hot flashes, *Cleve Clin J Med* 71:578, 2004.
- Women's Health Initiative Investigators: Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial, *JAMA* 288:321, 2002.



## BASIC INFORMATION

### DEFINITION

The human immunodeficiency virus (HIV) is a retrovirus that is responsible for causing acquired immunodeficiency syndrome (AIDS). HIV infection does not necessarily mean a person has AIDS.

### SYNOMYNS

AIDS: The result of progressive HIV infection in which a person has a weakened immune system and meets specific diagnostic criteria (See "Acquired Immunodeficiency Syndrome" in Section I.)

#### ICD-9CM CODES

042.9 HIV, unspecified  
044.9 HIV, unspecified

#### ICD-10CM CODES

B20 Human immunodeficiency virus [HIV]

### EPIDEMIOLOGY & DEMOGRAPHICS (IN U.S.)

- There are an estimated 1.1 million people infected with HIV in the United States, with approximately 1 out of 6 (15.8%) who do not know they are infected.
- In 2011, there were an estimated 49,273 new HIV infections according to the CDC.
- Greatest incidence is in men who have sex with men (MSM) and minority populations.

### PREDOMINANT RISK GROUPS

- Gay, bisexual, and other MSM are the groups most affected by HIV.
- In 2010, MSM accounted for 63% of all new infections according to the CDC.
- HIV disproportionately affects MSM of younger age and black/African American and Hispanic background.
- Heterosexual transmission and injection drug use accounted for 25% and 8% of new HIV infections in 2010, respectively.

### RACIAL DATA

- In 2010, blacks/African Americans accounted for 44% of new HIV infections despite being 12% of the U.S. population.
- In 2010, Hispanics/Latinos accounted for 21% of new HIV infections despite being 19% of the U.S. population.

### GENETICS

**Familial Disposition:** Individuals with deletions in the *CCR5* gene are immune from infection with macrophage tropic virus (the predominant virus in sexual transmission). Other genetic variants may contribute to rapid progression or long-term control of the virus once infected. One in 300 individuals infected with HIV is an "elite controller," which means they are able to maintain a normal CD4 count and undetectable viral load through immune control.

### Congenital Infection

- 80% of childhood cases are caused by peripartum infection, which may occur in utero, during delivery, or after delivery via breastfeeding.
- No specific congenital abnormalities are associated with HIV infection, although there is a higher risk of spontaneous abortion and low birth weight.

### Neonatal Infection

- May occur during delivery or via breastfeeding.
- Typically asymptomatic.

## PHYSICAL FINDINGS & CLINICAL PRESENTATION

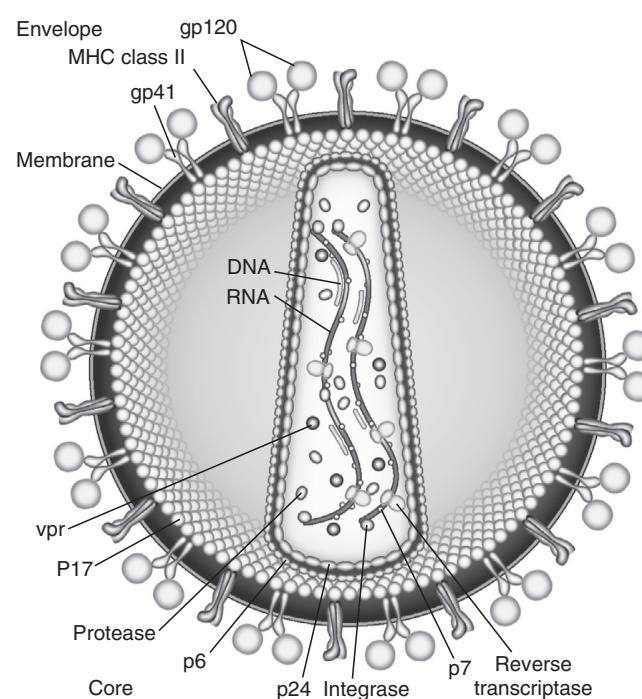
- Signs and symptoms are variable with stage of disease. "Stage 0" indicates a very early infection diagnosed when standard markers are converting from negative to positive.
- Acute HIV infection (0 to 3 months, usually within several weeks):
  - May cause a self-limited mononucleosis-like illness in 50% to 80% of individuals characterized by fever, sore throat, lymphadenopathy, headache, and a rash resembling roseola. Individuals may also be asymptomatic.
  - In a minority of acute cases, aseptic meningitis, Bell's palsy, or peripheral neuropathy may occur.
  - Rarely, opportunistic infections such as thrush or *Pneumocystis jiroveci* pneumonia (PJP) may occur.
- Chronic HIV infection is usually characterized by a prolonged asymptomatic phase followed by nonspecific symptoms of lymphadenopathy, fatigue, weight loss, diarrhea, and skin changes including seborrheic dermatitis, localized herpes zoster, and/or fungal infection.

- Advanced disease is characterized by AIDS-associated diseases, including infections and malignancies (see specific disorders).

- HIV infection in women may be associated with lower levels of viral load at comparable degrees of immunosuppression when compared with men. Furthermore, women may, on average, have higher CD4 counts at the time of HIV diagnosis.
- Another special consideration in women infected with HIV is the high incidence of human papillomavirus (HPV) co-infection and risk for cervical cancer. HIV-positive women should be screened for cervical cancer twice in the first year and then annually thereafter if pap smears are normal.
- Co-infection with HIV and hepatitis C is common because of similar transmission risk. Hepatitis C is most commonly transmitted by contaminated needles or blood exposure. Hepatitis C can be transmitted by sex, but the risk is low. Patients with HIV and hepatitis C progress faster to cirrhosis. Patients may already have signs of advanced liver disease at the time of diagnosis.

### ETIOLOGY

- HIV is a single-stranded RNA retrovirus (Figure H1-64) that is categorized as type 1 or 2.



**FIGURE H1-64 Structure of the HIV-1 virion.** The viral envelope is formed from the host cell membrane, into which the HIV-1 envelope proteins gp41 and gp120 have been inserted and may include several host cell proteins, most significantly the major histocompatibility complex class II proteins. The matrix between the envelope and the core is formed predominantly from gag protein p17. The core contains the viral RNA, closely associated with gag protein p7, in addition to RT and integrase. It has also been proven that virions contain complementary DNA, as shown, synthesized by the RT. The major structural proteins of the core are gag proteins p24 and p6. Also present within the virion are the protease and two cleavage products from the gag precursor protein (p1 and p2, not shown) of undetermined position within the virion. Viral protein R (Vpr) is also packaged in the virion and is thought to be localized within the core, as shown. (From Mandell GL et al: *Principles and practice of infectious diseases*, ed 7, Philadelphia, 2010, Saunders.)

- HIV-1 was derived from transmission of a simian immunodeficiency virus (SIV) from chimpanzees in Central Africa; HIV-2 was derived from an SIV found in sooty mangabey monkeys from West Africa.
- HIV-1 is the predominant pathogenic retrovirus in human populations; HIV-2 has limited distribution (primarily West Africa) and tends to progress less rapidly than HIV-1. HIV-2 should be considered in individuals from West Africa or if sexual partners are from West Africa.
- HIV-1 is transmitted by sexual contact, shared needles, blood transfusion, or from mother to child during pregnancy, delivery, or breastfeeding.
- Primary target of infection: CD4 lymphocytes.
- Direct central nervous system (CNS) involvement: manifests as encephalopathy, myelopathy, or neuropathy in advanced cases.
- Renal failure, rheumatologic disorders, thrombocytopenia, or cardiac abnormalities may be seen in association with HIV-1.

## Dx DIAGNOSIS

### DIFFERENTIAL DIAGNOSIS

- Acute HIV infection: often diagnosed or confused with mononucleosis or other respiratory viral infections
- Late symptoms: similar to those produced by other wasting/chronic illnesses such as neoplasms, tuberculosis (TB), disseminated fungal infection (such as *Candida*), malabsorption, or depression
- HIV-related encephalopathy: confused with Alzheimer's disease or other causes of chronic dementia (cognitive impairment in HIV infection is described in Section II); myelopathy and neuropathy possibly resembling other demyelinating diseases such as multiple sclerosis.

### WORKUP

Since the debut of HIV/AIDS in the 1980s, diagnosis has been established by testing for antibodies to the virus. The Centers for Disease Control and Prevention (CDC) is now recommending routine testing for patients in all health care settings unless the patient declines (opt-out screening). This includes routine testing of pregnant women. It is also recommended that separate written consent should no longer be required, although by law this is being addressed on a state-by-state basis. Generally, all persons aged 13–64 should undergo HIV testing at least once and more frequently (at least once a year) if sexually active.

- An FDA-approved at-home rapid HIV screening test is now available. It uses swabs of oral fluids from upper and lower gums. A positive test requires confirmatory testing in the office. Negative home tests should be repeated within 3 months.

### LABORATORY TESTS

HIV antibodies are detected by a two-step technique:

- ELISA (enzyme-linked immunosorbent assay), which is a sensitive screening test.
- Confirmation of positive ELISA tests with more specific assays. The classic confirmatory test

is the Western blot, but this is not commonly used anymore.

- Screening ELISA antibody tests will measure HIV-1 and HIV-2 antibodies. Confirmatory tests will generally differentiate between HIV-1 and HIV-2 as well. However, the viral load assays (HIV RNA PCR) are specific only for HIV-1.
- Baseline viral resistance testing is recommended for all newly diagnosed patients with HIV to guide choice of antiretroviral therapy (ART).
- The CD4 count and HIV RNA polymerase chain reaction (PCR) should be measured in all patients.
- The CD4 count is a marker of current immune status.
- The HIV RNA PCR (viral load) is predictive of disease progression.
- Rapid serologic tests have been increasingly used and are useful in specific settings: occupational exposures, pregnant women in labor without previous testing, and patients in high seroprevalence areas (for immediate results). Specimens are either blood or saliva and results are given within 1–20 min. Although sensitivity is high (99%), false-positive tests are more common in low seroprevalence populations. Thus, all positive results must be confirmed with standard serology.
- Early during infection (i.e., acute HIV infection), standard antibody tests may be negative

("window period"). The standard for diagnosing HIV during acute HIV infection is by testing for HIV RNA (viral load).

- In 2014, the CDC released a revised surveillance case definition for HIV infection. This information has been added in the EBM section of this topic.

**Fig. H1-65** describes the immunologic response to HIV infection.

## Rx TREATMENT

### NONPHARMACOLOGIC THERAPY

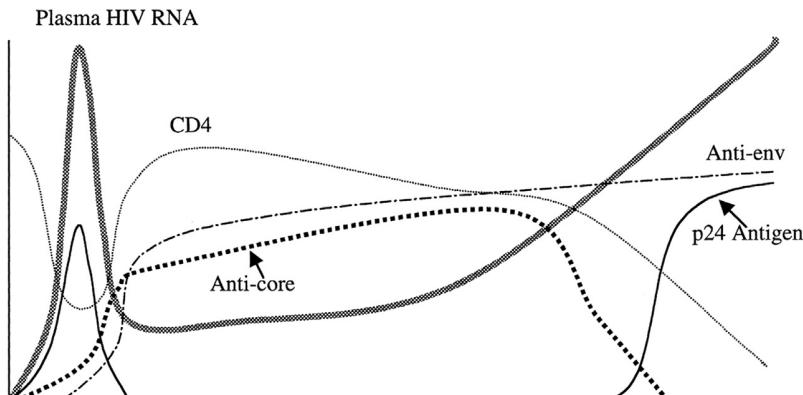
Maintenance of adequate nutrition

### ACUTE GENERAL Rx

Acute management of opportunistic infections and malignancies (see AIDS-associated disorders, "Pneumocystis jiroveci" Pneumonia," "Cryptococcosis," "Tuberculosis," "Toxoplasmosis" elsewhere in this text.)

### CHRONIC Rx

All HIV-infected patients should be considered for ART regardless of CD4 cell count. The benefit of ART is well established in preventing progression to AIDS and associated comorbidities. **Table H1-33** describes HIV treatment guidelines of the Department of Health and Human Services (DHHS) ([www.aidsinfo.nih.gov/guidelines](http://www.aidsinfo.nih.gov/guidelines)).



**FIGURE H1-65 Course of human immunodeficiency virus infection.** (From Mandell GL [ed]: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*, ed 6, New York, 2005, Churchill Livingstone.)

### TABLE H1-33 When to Initiate Antiretroviral Therapy (ART) in Treatment-Naïve Patients

ART should be initiated in all patients with a history of an AIDS-defining illness or with a CD4 count of <350 cells/mm<sup>3</sup> (AI).

ART is also recommended for patients with CD4 counts between 350 and 500 cells/mm<sup>3</sup> (AI).

ART is recommended for patients with CD4 counts greater than 500 cell/mm<sup>3</sup> (BII).

ART should also be initiated, regardless of CD4 count, in patients with the following conditions: HIV-associated nephropathy (HIVAN) and HBV coinfection when treatment of HBV is indicated (AI).

A combination ARV drug regimen is also recommended for pregnant women who are not otherwise on treatment, with the goal to prevent perinatal transmission (AI).

Patients initiating ART should be willing and able to commit to lifelong treatment and should understand the benefits and risks of therapy and the importance of adherence.

Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy based on clinical and/or psychosocial factors.

Other considerations for initiation of antiretroviral therapy are described in Table H1-34. Prophylaxis to prevent first episode of HIV-related opportunistic disease is described in Table H1-35.

- Therapy is strongly recommended for all patients with symptomatic established HIV disease regardless of the CD4 count. Symptomatic HIV disease is defined as the presence of any of the following: thrush, vaginal candidiasis, herpes zoster, peripheral neuropathy, bacillary angiomatosis, cervical dysplasia in situ, constitutional symptoms such as fever or diarrhea for more than 1 month, ITP, PID, or listeriosis.
- In asymptomatic individuals, ART is now recommended regardless of CD4 cell counts. The updated recommendations are due to the safety and benefit of newer antivirals in preventing AIDS and decreasing both morbidity and mortality. Earlier treatment may also help reduce transmission of the virus to others due to reductions in viral loads.
- ART generally consists of using a 3-drug regimen to treat HIV infection. Classes of antiretrovirals include:
  - Nucleoside/nucleotide reverse transcriptase inhibitor (NRTI): zidovudine (AZT), lamivudine (3TC), emtricitabine (FTC), tenofovir (TDF), abacavir (ABC), stavudine (D4T), or didanosine (DDI).
  - Protease inhibitors (PI): lopinavir/ritonavir, atazanavir, fosamprenavir, darunavir, saquinavir, amprenavir, tipranavir, nelfinavir, and indinavir. These PIs may be "boosted" by ritonavir to increase levels.
  - Nonnucleoside reverse transcriptase inhibitors (NNRTI): Nevirapine, efavirenz, etravirine, delavirdine, or rilpivirine.
  - Integrase Inhibitors (II): Raltegravir, elvitegravir, and dolutegravir. Raltegravir is a first-line agent according to the DHHS guidelines.
  - Fusion Inhibitors: Enfuvirtide (T-20). This drug is administered through subcutaneous injections and is only used as part of a salvage regimen for individuals who have failed multiple other regimens.
  - CCR5 Inhibitors: Maraviroc. Before using this drug, a viral tropism assay should

**TABLE H1-34** Conditions Favoring More Rapid Initiation of Antiretroviral Therapy

Pregnancy
AIDS-defining conditions
Acute opportunistic infections
Lower CD4 counts (e.g., <200 cells/mm <sup>3</sup> )
Rapidly declining CD4 counts (e.g., >100 cells/mm <sup>3</sup> decrease per year)
Higher viral loads (e.g., >100,000 copies/ml)
HIV-associated nephropathy
Hepatitis B/C virus (HBV/HCV) coinfection

Modified from Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. March 27, 2012. <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>.

be checked to determine if the virus uses the CCR5 co-receptor to infect cells. If the virus uses the CXCR4 co-receptor, this drug will not be effective.

- Adding a fourth drug to the three-drug regimen does not improve viral suppression or outcomes and is not recommended. Treatment interruptions based upon CD4 responses appear harmful in recent comparative studies versus standard continuous treatment protocols and should be avoided. Antiretroviral regimens for initial therapy are summarized in Table H1-36.
  - Typical initial dosing regimen consists of two NRTIs and either a NNRTI, PI, or II. Data support inclusion of lamivudine or emtricitabine as one of the two NRTIs.
  - Standard NRTIs include:
    - Truvada (tenofovir/emtricitabine) 1 tablet once daily.
    - Tenofovir: Individuals with underlying renal dysfunction or requiring other nephrotoxic agents may be at increased risk of renal toxicity.
    - Epzicom (abacavir/lamivudine) 1 tablet once daily
  - Abacavir: may be associated with increased risk of myocardial infarction. Before using this drug, individuals should be checked for HLA-B\*5701. Individuals with this allele are at higher risk of serious hypersensitivity reactions and this drug should be avoided.
  - Combivir (Zidovudine/lamivudine) 1 tablet twice daily
  - Zidovudine: Associated with lipodystrophy and anemia. GI and CNS side effects.
- Standard Backbone Regimens include:
- NNRTIs
    - Efavirenz 600 mg daily: not recommended for women in the first trimester or those who are contemplating pregnancy. This is considered the preferred agent within the class.
    - Nevirapine 200 mg two times a day: avoid with CD4 count >250 in men and >350 in women because of the risk of hepatitis. The newer agent rilpivirine had higher virologic failures and should be considered an alternative agent.
    - Etravirine 200 mg two times a day: This drug is generally used in patients that have failed other regimens. Etravirine retains activity in many patients that have developed resistance against efavirenz and nevirapine.
  - PIs (ritonavir boosted)
    - Lopinavir/ritonavir (200 mg/50 mg) 2 tablets twice a day (or 4 tablets once a day): most likely to cause diarrhea and has the greatest negative effect on triglyceride levels.
    - Atazanavir and ritonavir (300 mg and 100 mg) 2 tablets a day: lower pill burden, but use with caution with acid reducing agents—can alter absorption. This is considered a preferred PI regimen within the DHHS guidelines.
    - Fosamprenavir and ritonavir (700 mg and 100 mg) 2 tablets twice a day (or 4 tablets once a day): cannot take fosamprenavir with sulfa allergy.
  - Darunavir and ritonavir: 800 mg and 100 mg a day. This is considered a preferred PI regimen within the DHHS guidelines.
  - Saquinavir and ritonavir.
  - All these drugs have their own unique, as well as class-specific, side effects and require careful follow-up to achieve optimal antiviral effects. Compliance with the drug regimen and tolerance of common side effects are critically important to maintain drug efficacy. The FDA has approved Triumeq, a fixed-dose combination of the integrase strand inhibitor dolutegravir and the NRTIs abacavir and lamivudine, for once-daily treatment of HIV-1 infection. Antiviral response should be monitored by baseline HIV viral load and CD4 count and repeat measurement at 2 and 4 weeks into treatment and then periodically (every 3 to 6 months) to ensure viral suppression.
  - All patients should have genotypic resistance testing upon entry into medical care and before initiation of ART.
  - In experienced patients, an antiretroviral regimen should be constructed based on past antiretroviral use and the results of genotypic or phenotypic testing.
  - Patients with a CD4 count <200/mm<sup>3</sup> should be given preventive therapy for PJP (see "*Pneumocystis jirovecii* [*P. carinii*] Pneumonia").
  - Evaluation of chronic diarrhea in patients with HIV is described in the AIDS topic in Section I.
  - Criteria for discontinuing and restarting opportunistic infection prophylaxis for adults and adolescents with HIV infection is described in Table H1-37.
  - HIV infection in a pregnant woman poses special challenges and considerations. Appropriate and timely ART given to mother and newborn has been shown to dramatically reduce the risk of perinatal transmission of HIV. The goal of therapy is to achieve an undetectable viral load. For HIV-infected pregnant women who are already receiving ART: (1) Continue therapy if suppressing viral replication, but avoid use of efavirenz in the first trimester (substitution is recommended in the first trimester); (2) If viremia on therapy, genotypic testing is recommended; (3) Nevirapine should be continued, regardless of CD4 count, if there is viral suppression. For HIV-infected pregnant women who have never received ART: (1) Women who require ART for their own health should start on ART in the first trimester. Most antiretrovirals are safe in pregnancy, however, efavirenz should be avoided because of teratogenicity (Class D), DDI and D4T should be avoided (potential of lactic acidosis), and some protease inhibitors may be dose-altered in pregnancy. Nevirapine should not be initiated in an antiretroviral-naïve pregnant patient with CD4 counts >250 because of the risk of hepatotoxicity. (2) Women who do not need ART for their own health should also initiate three-drug therapy, but may do so at the end of the first trimester.

**TABLE H1-35** Prophylaxis to Prevent First Episode of HIV-related Opportunistic Disease

Pathogen	Indication	First Choice	Alternative
<i>Pneumocystis jirovecii</i> pneumonia (PJP, previously referred to as <i>Pneumocystis carinii</i> , PCP)	CD4 <sup>+</sup> count <200 cells/mm <sup>3</sup> or oropharyngeal candidiasis CD4 <sup>+</sup> <14% or history of AIDS-defining illness CD4 <sup>+</sup> count >200 but <250 cells/mm <sup>3</sup> if monitoring CD4 <sup>+</sup> count every 1-3 mo is not possible	Trimethoprim-sulfamethoxazole (TMP-SMX) double-strength PO daily; or single-strength daily	TMP-SMX 1 double-strength PO 3 times weekly; or Dapsone 100 mg PO daily or 50 mg PO bid; or Aerosolized pentamidine 300 mg via Respigrad II nebulizer every month; or Atovaquone 1500 mg PO daily
<i>Toxoplasma gondii</i> encephalitis	<i>Toxoplasma</i> IgG-positive patients with CD4 <sup>+</sup> count <100 cells/mm <sup>3</sup> Seronegative patients receiving PCP prophylaxis not active against toxoplasmosis should have <i>Toxoplasma</i> serology retested if CD4 <sup>+</sup> count declines to <100 cells/mm <sup>3</sup> . Prophylaxis should be initiated if seroconversion occurred.	TMP-SMX, 1 double-strength PO daily	TMP-SMX 1 double-strength PO 3 times weekly; or TMP-SMX 1 single-strength PO daily; or Dapsone 50 mg PO daily + pyrimethamine 50 mg PO weekly + leucovorin 25 mg PO weekly; or Dapsone 200 mg PO weekly + pyrimethamine 75 mg PO weekly + leucovorin 25 mg PO weekly; Rifampin (RIF) 600 mg PO daily × 3-4 mo; or Rifabutin (RFB) 300 mg once daily for 4 mo. Be careful of drug interactions with these medications (PIs and NNRTIs).
<i>Mycobacterium tuberculosis</i> infection (TB) (treatment of latent TB infection or LTBI)	(1) Diagnostic test for LTBI, no evidence of active TB, and no prior history of treatment for active or latent TB (2) Diagnostic test for LTBI, but close contact with a person with infectious pulmonary TB and no evidence of active TB (3) A history of untreated or inadequately treated healed TB (i.e., old fibrotic lesions) regardless of diagnostic tests for LTBI and no evidence of active TB	Isoniazid (INH) 300 mg PO daily or 900 mg PO twice weekly for 9 mo—both plus pyridoxine 50 mg PO daily; or For persons exposed to drug-resistant TB, selection of drugs after consultation with public health authorities	RFB 300 mg PO daily (dosage adjustment based on drug-drug interactions with antiretroviral therapy); rule out active TB before starting RFB
Disseminated <i>Mycobacterium avium complex</i> (MAC) disease	CD4 <sup>+</sup> count <50 cells/mm <sup>3</sup> —after ruling out active MAC infection	Azithromycin 1200 mg PO once weekly; or Clarithromycin 500 mg PO bid; or Azithromycin 600 mg PO twice weekly 23-valent PPV 0.5 ml IM × 1 Revaccination every 5 yr may be considered	
<i>Streptococcus pneumoniae</i> infection	CD4 <sup>+</sup> count >200 cells/mm <sup>3</sup> and no receipt of pneumococcal vaccine in the past 5 yr CD4 <sup>+</sup> count <200 cells/mm <sup>3</sup> —vaccination can be offered In patients who received polysaccharide pneumococcal vaccination (PPV) when CD4 <sup>+</sup> count <200 cells/mm <sup>3</sup> but has increased to >200 cells/mm <sup>3</sup> in response to antiretroviral therapy	Inactivated influenza vaccine 0.5 ml IM annually Itraconazole 200 mg PO daily	
Influenza A and B virus infection	All HIV-infected patients		
<i>Histoplasma capsulatum</i> infection	CD4 <sup>+</sup> count ≤150 cells/mm <sup>3</sup> and at high risk because of occupational exposure or live in a community with a hyperendemic rate of histoplasmosis (>10 cases/100 patient-yr)		
Coccidioidomycosis	Positive IgM or IgG serologic test result in a patient from a disease-endemic area; and CD4 <sup>+</sup> count <250 cells/mm <sup>3</sup>	Fluconazole 400 mg PO daily Itraconazole 200 mg PO bid	
Varicella-zoster virus (VZV) infection	<i>Pre-exposure prevention:</i> Patients with CD4 <sup>+</sup> count ≥200 cells/mm <sup>3</sup> who have not been vaccinated, have no history of varicella or herpes zoster, or who are seronegative for VZV <i>Note:</i> Routine VZV serologic testing in HIV-infected adults is not recommended. <i>Postexposure—close contact with a person who has active varicella or herpes zoster:</i> For susceptible patients (those who have no history of vaccination or of either condition, or are known to be VZV seronegative)	<i>Pre-exposure prevention:</i> Primary varicella vaccination (Varivax), 2 doses (0.5 ml SC) administered 3 mo apart If vaccination results in disease because of vaccine virus, treatment with acyclovir is recommended. <i>Postexposure therapy:</i> Varicella-zoster immune globulin (VarizIG) 125 IU per 10 kg (maximum of 625 IU) IM, administered within 96 hr after exposure to a person with active varicella or herpes zoster <i>Note:</i> As of June 2007, VarizIG can be obtained only under a treatment IND (1-800-843-7477, FFF Enterprises). HPV quadrivalent vaccine 0.5 ml IM mo 0, 2, and 6	VZV-susceptible household contacts of susceptible HIV-infected persons should be vaccinated to prevent potential transmission of VZV to their HIV-infected contacts. <i>Alternative postexposure therapy:</i> Postexposure varicella vaccine (Varivax) 0.5 ml SC × 2 doses, 3 mo apart if CD4 <sup>+</sup> count >200 cells/mm <sup>3</sup> ; or Preemptive acyclovir 800 mg PO 3×/day for 5 days These two alternatives have not been studied in the HIV population.
Human papillomavirus (HPV) infection	Women aged 11-26 yr. Men aged 11-21 yr		

Modified from Centers for Disease Control and Prevention. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Disease Society of America, *MMWR Morb Mortal Wkly Rep* 58(RR-4), 2009.

Continued on following page

**TABLE H1-35** Prophylaxis to Prevent First Episode of HIV-related Opportunistic Disease—(Continued)

Pathogen	Indication	First Choice	Alternative
Hepatitis A virus (HAV) infection	HAV-susceptible patients with chronic liver disease or who are injection-drug users, or men who have sex with men. Certain specialists might delay vaccination until CD4 <sup>+</sup> count >200 cells/mm <sup>3</sup> .	Hepatitis A vaccine 1 ml IM × 2 doses—at 0 and 6–12 mo IgG antibody response should be assessed 1 mo after vaccination; nonresponders should be revaccinated	
Hepatitis B virus (HBV) infection	All HIV patients without evidence of prior exposure to HBV should be vaccinated with HBV vaccine, including patients with CD4 <sup>+</sup> count <200 cells/mm <sup>3</sup> .  <i>Patients with isolated anti-HBC:</i> consider screening for HBV DNA before vaccination to rule out occult chronic HBV infection  <i>Vaccine nonresponders:</i> Defined as anti-HBs <10 IU/ml 1 mo after a vaccination series  For patients with low CD4 <sup>+</sup> count at the time of first vaccination series, certain specialists might delay revaccination until after a sustained increase in CD4 <sup>+</sup> count with antiretroviral therapy.	Hepatitis B vaccine IM (Engerix-B 20 µg/ml or Recombivax HB 10 µg/ml) at 0, 1, and 6 mo  Anti-HBs should be obtained 1 mo after completion of the vaccine series.  Revaccinate with a second vaccine series.	Some experts recommend vaccinating with 40-µg doses of either vaccine.  Some experts recommend revaccinating with 40-µg doses of either vaccine.

**TABLE H1-36** What Antiretroviral Regimen to Choose for Initial Therapy

Preferred Regimens	Comments
NNRTI-based regimen EFV/TDF/FTC	EFV should not be used during the first trimester of pregnancy or in women trying to conceive or not using effective and consistent contraception.
PI-based regimens (in alphabetical order) ATV/r + TDF/FTC DRV/r (once daily) + TDF/FTC	ATV/r should not be used in patients who are on proton pump inhibitors or other antacids.
Integrase inhibitor-based regimen RAL + TDF/FTC Dolutegravir + TDF/FTC Elvitegravir + cobicistat + TDF/FTC	
Preferred regimen for pregnant women LPV/r (twice daily) + ZDV/3TC	
Alternative Regimens	Comments
NNRTI-based regimens (in alphabetical order) EFV + ABC/3TC RPV/TDF/FTC RPV + ABC/3TC	NVP should not be used in patients with moderate to severe hepatic impairment (Child-Pugh B or C). Should not be used in women with pre-treatment CD4 >250 cells/mm <sup>3</sup> or men with CD4 >400 cells/mm <sup>3</sup>
PI-based regimens (in alphabetical order) ATV/r + ABC/3TC DRV + ABC/3TC	ABC should not be used in patients who test positive for HLA-B*5701 Use with caution in patients with high risk of cardiovascular disease or with pretreatment HIV RNA >100,000 copies/mL Once-daily LPV/r is not recommended in pregnant women.
FPV/r (once or twice daily) + either ABC/3TC or TDF/FTC LPV/r (once or twice daily) + either [(ABC or ZDV)/3TC] or TDF/FTC	
Integrase inhibitor-based regimens RAL + ABC/3TC Dolutegravir + ABC/3TC	
Acceptable Regimens	
EFV + AZT/3TC NVP + TDF/FTC or ABC/3TC or AZT/3TC RPV + AZT/3TC ATV + ABC/3TC or AZT/3TC ATV/r + AZT/3TC DRV/r + AZT/3TC FPV/r + AZT/3TC LPV/r + AZT/3TC RAL + AZT/3TC MVC + AZT/3TC or TDF/FTC or ABC/3TC	

*3TC, Lamivudine; ABC, abacavir; ATV, atazanavir; ddI, didanosine; DRV, darunavir; Efv, efavirenz; FPV, fosamprenavir; FTC, emtricitabine; INSTI, integrase strand transfer inhibitor; LPV, lopinavir; MRV, maraviroc; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleos(t)ide reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; r, low dose ritonavir; RAL, raltegravir; RPV, rilpivirine; S0V, saquinavir; TDF, tenofovir; ZDV, zidovudine.*The following combinations in the recommended list are available as fixed-dose combination formulations: ABC/3TC, Efv/TDF/FTC, LPV/r, TDF/FTC, RPV/TDF/FTC, and ZDV/3TC.

Modified from Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services 1-161, 2012. <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>.

**TABLE H1-37** Criteria for Discontinuing and Restarting Opportunistic Infection Prophylaxis for Adults and Adolescents with Human Immunodeficiency Virus Infection

Opportunistic Infection	Criteria for Discontinuing Primary Prophylaxis	Criteria for Restarting Primary Prophylaxis	Criteria for Discontinuing Secondary Prophylaxis/Chronic Maintenance Therapy	Criteria for Restarting Secondary Prophylaxis/Chronic Maintenance Therapy
<i>Pneumocystis pneumonia (PJP)</i>	CD4 <sup>+</sup> count >200 cells/mm <sup>3</sup> for >3 mo in response to ART	CD4 <sup>+</sup> count <200 cells/mm <sup>3</sup>	CD4 <sup>+</sup> count increased from <200 cells/mm <sup>3</sup> to >200 cells/mm <sup>3</sup> for ≥3 mo in response to ART If PJP is diagnosed when CD4 <sup>+</sup> count >200 cells/mm <sup>3</sup> , prophylaxis should probably be continued for life regardless of CD4 <sup>+</sup> count rise in response to ART.	CD4 <sup>+</sup> count <200 cells/mm <sup>3</sup> , or if PCP recurred at a CD4 <sup>+</sup> count >200 cells/mm <sup>3</sup>
<i>Toxoplasma gondii</i> encephalitis (TE)	CD4 <sup>+</sup> count >200 cells/mm <sup>3</sup> for >3 mo in response to ART	CD4 <sup>+</sup> count <100–200 cells/mm <sup>3</sup>	Successfully completed initial therapy, remain asymptomatic of signs and symptoms of TE, and CD4 <sup>+</sup> count >200 cells/mm <sup>3</sup> for >6 mo in response to ART	CD4 <sup>+</sup> count <200 cells/mm <sup>3</sup>
Microsporidiosis	Not applicable	Not applicable	No signs and symptoms of non-ocular microsporidiosis and CD4 <sup>+</sup> count >200 cells/mm <sup>3</sup> for >6 mo in response to ART Patients with ocular microsporidiosis should be on therapy indefinitely regardless of CD4 <sup>+</sup> count.	No recommendation
Disseminated <i>Mycobacterium avium complex</i> (MAC) disease	CD4 <sup>+</sup> count >100 cells/mm <sup>3</sup> for ≥3 mo in response to ART	CD4 <sup>+</sup> count <50 cells/mm <sup>3</sup>	If fulfill the following criteria Completed ≥12 mo therapy, and No signs and symptoms of MAC, and Have sustained (≥6 mo) CD4 <sup>+</sup> count >100 cells/mm <sup>3</sup> in response to ART	CD4 <sup>+</sup> count <100 cells/mm <sup>3</sup>
Bartonellosis	Not applicable	Not applicable	If fulfill the following criteria Received 3–4 mo of treatment CD4 <sup>+</sup> count >200 cells/mm <sup>3</sup> for ≥6 mo Certain specialists would discontinue therapy only if <i>Bartonella</i> titers have also decreased by fourfold.	No recommendation
Mucosal candidiasis	Not applicable	Not applicable	If used, reasonable to discontinue when CD4 <sup>+</sup> count >200 cells/mm <sup>3</sup>	No recommendation
Cryptococcal meningitis	Not applicable	Not applicable	If fulfill the following criteria Completed course of initial therapy Remain asymptomatic of cryptococcosis CD4 <sup>+</sup> count ≥200 cells/mm <sup>3</sup> for >6 mo in response to ART Certain specialists would perform a lumbar puncture to determine if cerebrospinal fluid is culture and antigen negative before stopping therapy.	CD4 <sup>+</sup> count <200 cells/mm <sup>3</sup>
<i>Histoplasma capsulatum</i> infection	If used, CD4 <sup>+</sup> count >150 cells/mm <sup>3</sup> for 6 mo on ART	For patients at high risk for acquiring histoplasmosis, restart at CD4 <sup>+</sup> count ≤150 cells/mm <sup>3</sup> .	If fulfill the following criteria Received itraconazole for ≥1 yr Negative blood cultures CD4 <sup>+</sup> count >150 cells/mm <sup>3</sup> for ≥6 mo in response to ART Serum <i>Histoplasma</i> antigen <2 units	CD4 <sup>+</sup> count ≤150 cells/mm <sup>3</sup>
Coccidioidomycosis	If used, CD4 <sup>+</sup> count ≥250 cells/mm <sup>3</sup> for ≥6 mo	If used, restart at CD4 <sup>+</sup> count <250 cells/mm <sup>3</sup> Receiving ART	<b>Only for patients with focal coccidioidal pneumonia:</b> Clinically responded to ≥12 mo of antifungal therapy CD4 <sup>+</sup> count >250 cells/mm <sup>3</sup> Receiving ART Suppressive therapy should be continued indefinitely, even with increase in CD4 <sup>+</sup> count on ART for patients with diffuse pulmonary, disseminated, or meningeal diseases.	No recommendation
Cytomegalovirus retinitis	Not applicable	Not applicable	CD4 <sup>+</sup> count >100 cells/mm <sup>3</sup> for >3–6 mo in response to ART. Therapy should be discontinued only after consultation with an ophthalmologist, taking into account magnitude and duration of CD4 <sup>+</sup> count increase, anatomic location of the lesions, vision in the contralateral eye, and the feasibility of regular ophthalmologic monitoring. Routine (every 3 mo) ophthalmologic follow-up is recommended for early detection of relapse or immune restoration uveitis.	CD4 <sup>+</sup> count <100 cells/mm <sup>3</sup>
<i>Isospora belli</i> infection	Not applicable	Not applicable	Sustained increase in CD4 <sup>+</sup> count to >200 cells/mm <sup>3</sup> for >6 mo in response to ART and without evidence of <i>I. belli</i> infection	No recommendation

Modified from Centers for Disease Control and Prevention. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Disease Society of America. *MMWR Morb Mortal Wkly Rep* 58(RR-4), 2009.

- Zidovudine (AZT) is recommended as a component of ART.
- Therapy should continue through the baby's birth. Zidovudine is given intravenously at the time of labor, regardless of whether it is an existing component of her three-drug regimen. In women with viral loads persistently >1000 copies/ml despite appropriate ART, cesarean section may further lower risk of transmission. Zidovudine (AZT) should also be given to the newborn for the first 6 weeks of life, and mothers should completely avoid nursing.

## DISPOSITION

- Ongoing care consisting of frequent medical evaluations and monitoring of CD4 counts and HIV viral loads.
- Long-term care focused on providing up-to-date ART and prophylaxis of PJP and other opportunistic infections, as well as early detection of complications (see Section III).
- Ongoing assessment for cardiovascular risk and other primary prevention interventions.
- Screening for hepatitis A, B, and C. Treatment when indicated. Drugs such as tenofovir and lamivudine have activity against both HIV and

hepatitis B and may be used in patients with co-infection.

- Vaccinations including hepatitis A and B (when susceptible), Pneumovax, tetanus/diphtheria/pertussis, and influenza. **Box H1-9** summarizes vaccinations in HIV-positive adults.
- Yearly screening for other sexually transmitted infections (chlamydia, gonorrhea, syphilis).
- Consideration of AIDS (lymphomas, HPV) and non-AIDS related (screening for general population, age-specific cancers).

## REFERRAL

To a physician knowledgeable and experienced in the management of HIV infection and its complications.

## PREVENTION

- Truvada may be used as preexposure prophylaxis (PrEP). Individual who are HIV negative may take Truvada once a day to prevent HIV infection. PrEP has been demonstrated to be effective in MSM, heterosexuals, and injection drug users. Individuals on PrEP should be monitored every 3 months for renal dysfunction, HIV status, and adherence.

- Post-exposure prophylaxis (PEP) is an effective prevention intervention for individuals exposed to HIV infection, either occupationally or through a sexual exposure. PEP should be taken within 72 hours of an exposure and continued for 28 days. Baseline HIV status, renal function, hepatitis B/C, and liver function should be assessed. The recommended first-line regimen is raltegravir and Truvada.

## PEARLS & CONSIDERATIONS

### COMMENTS

- HIV chemoprophylaxis after occupational exposure is described in Section V.
- Analysis of the impact of ART indicates that ART has saved at least 3 million years of life since the introduction into medicine more than 10 years ago.
- ART should be initiated in all HIV-infected individuals regardless of CD4 cell counts.
- Trials involving antiretroviral chemoprophylaxis before exposure for the prevention of HIV acquisition in MSM have shown that oral tenofovir disoproxil fumarate (FTC-TDF) provides protection against acquisition of HIV infection. This is known as *preexposure prophylaxis (PrEP)*. Detected blood levels strongly correlated with the prophylactic effect.
- ART in combination with avoidance of breastfeeding and elective cesarean section in women with viremia reduces risk for mother-to-child transmission.

## EBM EVIDENCE

Available at [www.expertconsult.com](http://www.expertconsult.com)

## SUGGESTED READINGS

Available at [www.expertconsult.com](http://www.expertconsult.com)

## RELATED CONTENT

Human Immunodeficiency Virus (HIV) Infection (Patient Information)

Acquired Immunodeficiency Syndrome (Related Key Topic)

AUTHOR: PHILIP A. CHAN, M.D., M.S.

## BOX H1-9 Vaccination in HIV-Positive Adults

### Generally Avoid

- VZV
- BCG
- Oral polio
- Oral typhoid

### Avoid if CD4+ Cells <200

- Yellow fever
- Measles

### Give Routinely

- Tetanus/diphtheria (or Tdap)
- Hepatitis B
- Streptococcus pneumoniae*
- Hib
- Influenza, yearly
- Hepatitis A

### Give if Indicated for Travel

- Typhoid Vi
- Meningococcal
- Polio, IPV
- Rabies
- Japanese encephalitis
- Tick-borne encephalitis

From Auerbach P: *Wilderness medicine, expert consult Premium Edition—Enhanced Online Features and Print*, Philadelphia, 2012, Saunders.



## EVIDENCE

Following extensive consultation and peer review, CDC and the Council of State and Territorial Epidemiologists have revised and combined the surveillance case definitions for human immunodeficiency virus (HIV) infection into a single case definition for persons of all ages (i.e., adults and adolescents aged  $\geq 13$  years and children aged  $<13$  years). The revisions were made to address multiple issues, the most important of which was the need to adapt to recent changes in diagnostic criteria. Laboratory criteria for defining a confirmed case now accommodate new multitest algorithms, including criteria for differentiating between HIV-1 and HIV-2 infection and for recognizing early HIV infection. A confirmed case can be classified in one of five HIV infection stages (0, 1, 2, 3, or unknown); early infection, recognized by a negative HIV test within 6 months of HIV diagnosis, is classified as stage 0, and acquired immunodeficiency syndrome (AIDS) is classified as stage 3. Criteria for stage 3 have been simplified by eliminating the need to differentiate between definitive and presumptive diagnoses of opportunistic illnesses. Clinical (nonlaboratory) criteria for defining a case for surveillance purposes have been made more practical by eliminating the requirement for information about laboratory tests. The surveillance case definition is intended primarily for monitoring the HIV infection burden and planning for prevention and care on a population level, not as a basis for clinical decisions for individual patients. CDC and the Council of State and Territorial Epidemiologists recommend that all states and territories conduct case surveillance of HIV infection using this revised surveillance case definition.

For the complete document, please visit <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6303a1.htm>.

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## BASIC INFORMATION

### DEFINITION

Huntington's disease is an autosomal dominant neurodegenerative disorder characterized by involuntary movements, psychiatric disturbance, and cognitive decline.

### SYNOMYS

Huntington's chorea

**ICD-9CM CODES**

333.4 Huntington's chorea

**ICD-10CM CODES**

G10 Huntington's disease

**EPIDEMIOLOGY & DEMOGRAPHICS**

**PEAK INCIDENCE:** Late 30s and 40s, with onsets from ages 2 to 70 yr

**PREVALENCE (IN U.S.):** 4.1 to 8.4 cases/100,000 persons

**PREDOMINANT SEX:** Female = male

**PREDOMINANT AGE:** Adulthood

**GENETICS:** Autosomal dominant

**PHYSICAL FINDINGS & CLINICAL PRESENTATION**

- Chorea: irregular, rapid, flowing, nonstereotyped involuntary movements. When there is a writhing quality, it is referred to as choreoathetosis. Chorea is present early on and tends to decrease in end stages of disease.
- Dancelike, lurching gait, often caused by chorea.
- Westphal variant: cognitive dysfunction, bradykinesia, and rigidity. This variant is more commonly seen in juvenile-onset Huntington's.
- Oculomotor abnormalities are common early on and include increased latency of response and insuppressible eye blinking.
- Psychiatric disorders (can be present early on): depression is commonly seen as well as obsessive-compulsive behaviors and aggression associated with impaired impulse control.

**ETOLOGY**

- Trinucleotide repeat disorder
- The responsible gene is the Huntington gene located on chromosome 4. Its function is not known.

**Dx DIAGNOSIS****DIFFERENTIAL DIAGNOSIS**

- Drug-induced chorea: dopamine, stimulants, anticonvulsants, antidepressants, and oral contraceptives have all been known to cause chorea.
- Sydenham's chorea: decreased incidence with decline of rheumatic fever.
- Benign hereditary chorea: autosomal dominant with onset in childhood; non-progressive and without associated dementia or behavioral problems.
- Senile chorea: possibly vascular in origin.
- Wilson's disease: autosomal recessive; tremor, dysarthria, and dystonia are more common presentations than chorea. A total of 95% of patients with neurologic manifestations will have Kayser-Fleischer rings.
- Postinfectious.
- Systemic lupus erythematosus: can be the presenting feature of lupus (rare).
- Chorea gravidarum: presents during first 4 to 5 mo of pregnancy and resolves after delivery.
- Paraneoplastic: seen most commonly in small-cell lung cancer and lymphoma.

**WORKUP**

Onset of symptoms in an individual with an established family history requires no additional investigation.

**LABORATORY TESTS**

- Genetic testing for CAG repeats
- If genetic tests are normal, obtain complete blood count with smear, erythrocyte sedimentation rate, electrolytes, serum ceruloplasmin, 24-hr urinary copper excretion, TFTs, antinuclear antibody, liver function tests, HIV, and ASO titer. Consider paraneoplastic markers.

**IMAGING STUDIES**

CT scan or MRI scan will show atrophy, most notably in the caudate and putamen. The cortex is involved to a lesser extent. A normal scan does not exclude the diagnosis.

**Rx TREATMENT****NONPHARMACOLOGIC THERAPY**

- Supportive counseling
- Physical and occupational therapy

- Home health care
- Genetic counseling

**CHRONIC Rx**

- Chorea does not need to be treated unless it is disabling.
- Tetrabenazine (TBZ) is approved by the FDA for the symptomatic treatment of chorea seen in Huntington's disease. It is a reversible inhibitor of the vesicle monoamine transporter type 2 (VMAT-2). It inhibits primarily dopamine and to a lesser degree serotonin and norepinephrine. Side effects include parkinsonism and severe depression.
- Neuroleptics, typical or atypical, can be used for symptomatic management of neuropsychiatric issues and chorea at low doses (e.g., haloperidol 1 to 10 mg/day).
- Amantadine (up to 300 to 400 mg divided tid).
- Depression with suicidal ideation is common; may improve with tricyclic antidepressants or SSRI

**DISPOSITION**

Relentless course of variable duration leading to progressive disability and death

**REFERRAL**

- Should refer to psychiatry and neurology for treatment of mood disorders and movement disorders
- Genetic counseling

**PEARLS & CONSIDERATIONS**

- Suicide rate is fivefold that of the general population.
- The number of repeats does correlate with age of onset but does not clearly correlate with disease severity. Interpretation of number of repeats is still difficult at this time; therefore it is debatable whether to disclose this information to patients.

**SUGGESTED READINGS**

Available at [www.expertconsult.com](http://www.expertconsult.com)

**RELATED CONTENT**

Huntington's Disease (Patient Information)

AUTHOR: FARIHA ZAHEER, M.D.

## SUGGESTED READINGS

- Bonelli RM et al.: Huntington's disease: present treatments and future therapeutic modalities, *Int Clin Psychopharmacol* 19:51, 2004.
- Greenamyre JT: Huntington's disease, making connections, *N Engl J Med* 356: 5, 2007.
- Higgins D: Chorea and its disorders, *Neuro Clin* 19(3):707, 2001.
- Walker FO: Huntington's disease, *Lancet* 369:218–228, 2007.



## BASIC INFORMATION

### DEFINITION

A hydrocele is a fluid collection in a serous scrotal space, usually between the layers of the tunica vaginalis (Fig. H1-66). A hydrocele that fills with fluid from the peritoneum is termed *communicating*. This is distinguished from a *noncommunicating* hydrocele by history of variation in size throughout the day and palpation of a thickened cord above the testicle on the affected side. A communicating hydrocele is a small inguinal hernia in which fluid, but not peritoneal structures, traverses the processus vaginalis. In noncommunicating hydrocele, the processus vaginalis was obliterated during development. An abdominoscrotal hydrocele is a rare variant of a hydrocele in which there is a large, tense hydrocele that extends into the lower abdominal cavity.

### ICD-9CM CODES

603.9 Hydrocele

### ICD-10CM CODES

N43.3 Hydrocele, unspecified

N43 Hydrocele and spermatocele

N43.0 Encysted hydrocele

N43.1 Infected hydrocele

N43.2 Other hydrocele

## PHYSICAL FINDINGS & CLINICAL PRESENTATION

### Symptoms:

- Scrotal enlargement
- Scrotal heaviness or discomfort radiating to the inguinal area
- Back pain

### Physical findings:

- Most hydroceles are smooth and nontender. Scrotal distention may make it difficult to

palpate the testis, but it is important to palpate the testis because some young men develop a hydrocele in association with a testis tumor

- Transillumination of the scrotum confirms the fluid-filled nature of the mass

### ETIOLOGY

Hydroceles may occur as a congenital abnormality in which the processus vaginalis fails to close. In this case an inguinal hernia is virtually always associated with the malformation. Congenital hydroceles are most common in infants (1%-2% of neonates have hydroceles) and children. In adults, hydroceles are more frequently caused by infection, tumor, or trauma. Infection of the epididymis often results in the development of a secondary hydrocele. Tropical infections such as filariasis may produce hydroceles.

## Dx DIAGNOSIS

### DIFFERENTIAL DIAGNOSIS

- Spermatocele
- Inguinoscrotal hernia
- Testicular tumor
- Varicocele
- Epididymitis

### IMAGING STUDIES

Scrotal ultrasound is useful to rule out a testicular tumor as the cause of the hydrocele (Fig. H1-67). The acute development of a hydrocele might be associated with the onset of epididymitis, testicular tumor, trauma, and torsion of a testicular appendage. An ultrasound of the scrotum may provide important diagnostic information.

## Rx TREATMENT

- No treatment if asymptomatic and testis is believed to be normal. Most congenital hydroceles resolve by 12 months of age following reabsorption of the hydrocele fluid.
- Surgical repair should be considered if the hydrocele is tense and large. Communicating hydroceles should be repaired in the same manner as an indirect hernia. The indications for repair of a noncommunicating hydrocele include failure to resolve and increase in size to one that is large and tense.
- Surgical correction is similar to a herniorrhaphy: an inguinal incision is made, the spermatic cord is identified, the hydrocele fluid is drained, and a high ligation of the processus vaginalis is performed.

## PEARLS & CONSIDERATIONS

- The long-term risk of a communicating hydrocele is the development of an inguinal hernia.
- An inguinal hernia/hydrocele is likely if compression of the fluid-filled mass completely reduces the hydrocele.

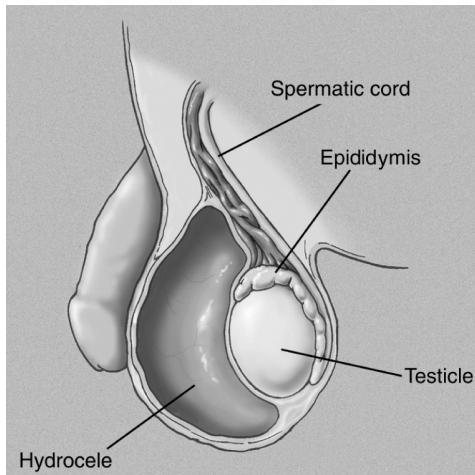
### SUGGESTED READINGS

Available at [www.expertconsult.com](http://www.expertconsult.com)

### RELATED CONTENT

Hydrocele (Patient Information)

AUTHOR: FRED F. FERRI, M.D.



**FIGURE H1-66** Schematic representation of the testicle, epididymis, spermatic cord, and a hydrocele. (From Lipshultz LI et al: *Urology and the primary care practitioner*, ed 3, Philadelphia, 2008, Elsevier.)



**FIGURE H1-67** Longitudinal ultrasound view of normal testis and moderate hydrocele. (From Grainger RG et al [eds.]: *Grainger & Allison's diagnostic radiology*, ed 4, London, 2001, Harcourt.)

**SUGGESTED READING**

Elder JD: Disorders and anomalies of the scrotal contents. In: (editor: Kliegman R.M.; et al.) *Nelson textbook of pediatrics*. ed 19, Saunders: Philadelphia.



## BASIC INFORMATION

### DEFINITION

Normal pressure hydrocephalus (NPH) is a syndrome of symptomatic hydrocephalus in the setting of normal cerebrospinal fluid (CSF) pressure. The classic clinical triad of NPH includes gait disturbance, cognitive decline, and incontinence.

### SYNONYMS

Occult hydrocephalus  
Extraventricular obstructive hydrocephalus  
Chronic hydrocephalus

#### ICD-9CM CODES

331.3 Communicating hydrocephalus

#### ICD-10CM CODES

G91.2 Normal pressure hydrocephalus

G91.8 Other hydrocephalus

### EPIDEMIOLOGY & DEMOGRAPHICS

**INCIDENCE:** The exact incidence is not known. In one study the incidence was found to be 5.5 per 100,000, but it may account for up to 5% of dementia in the U.S. Hospital discharge data suggest approximately 11,500 new cases diagnosed annually (may be overestimated). The prevalence of NPH may be as high as 14% among extended care facility patients.

**PREDOMINANT SEX:** Males = females

**PREDOMINANT AGE:** NPH is more common with increasing age.

### PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Gait difficulty: patients often have difficulty initiating ambulation, and the gait may be broad based and shuffling, with the appearance that the feet are stuck to the floor ("magnetic gait" or "frontal gait disorder").
- Cognitive decline: mental slowing, forgetfulness and inattention typically without agnosia, aphasia, or other cortical disturbances.
- Incontinence: initially may have urinary urgency; incontinence later develops. Fecal incontinence also occasionally occurs.
- Gegenhalten (paratonia) or other frontal lobe signs may be seen.

### ETOLOGY

- Approximately 50% of cases are idiopathic; the remaining cases have a variety of causes, including prior subarachnoid hemorrhage, meningitis, head trauma, or intracranial surgery.
- Symptoms are presumed to result from stretching of sacral motor and limbic fibers that lie near the ventricles as dilation occurs.



## DIAGNOSIS

### DIFFERENTIAL DIAGNOSIS

- Alzheimer's disease with extrapyramidal features
- Cognitive impairment in the setting of Parkinson's disease or parkinsonism-plus syndromes

- Diffuse Lewy body disease
- Frontotemporal dementia
- Cervical spondylosis with cord compromise in the setting of degenerative dementia
- Multi-infarct dementia
- HIV dementia

### WORKUP

- Large-volume lumbar puncture:
  - Mental status testing and time to walk a prespecified distance (usually 25 feet) are measured, followed by removal of 40 to 50 mL of CSF.
  - Retest of mental status and timed walking are done later (sometimes at 1 and 4 hr). Patients who have significant improvement in gait or mental status may have a better surgical outcome; those with mild or negative response can have variable outcomes.
  - Opening and closing pressure are measured; if pressure is elevated, alternative causes must be considered. Higher *normal*/pressure may predict a good outcome from CSF shunting.
- Measurement of CSF outflow resistance by an infusion test or CSF pressure monitoring is sometimes used to help predict surgical outcome. External lumbar drainage (ELD) is being used more commonly.

### LABORATORY TESTS

- CSF should be sent for routine fluid analysis to exclude other pathologies.
- CSF biomarkers may be useful in excluding Alzheimer's disease.
- The CSF protein lipocalin-type prostaglandin D synthase (L-PGDS) is being studied as a potential diagnostic biomarker in idiopathic NPH.

### IMAGING STUDIES

- CT scan or MRI can be used to document ventriculomegaly. The distinguishing feature of NPH is ventricular enlargement out of proportion to sulcal atrophy (Fig. EH1-68), and typically the frontal horn ratio exceeds 0.50. An algorithm for evaluation of patients with enlarged ventricles is described in Fig. EH1-69.
- MRI has advantages over CT, including better ability to visualize structures in the posterior fossa, visualize transependymal CSF flow (seen as periventricular hyperintensity), and document extent of white matter lesions. On MRI a flow void in the aqueduct and third ventricle ("jet sign"), thinning and elevation of the corpus callosum on sagittal images, rounding of the frontal horns, and a narrow CSF space at the high convexity/midline areas relative to Sylvian fissure size may be seen.
- Isotope cisternography and dynamic MRI studies have not been shown to be superior in predicting shunt outcome.

## Rx TREATMENT

There is no evidence that NPH can be effectively treated with medications.

### NONPHARMACOLOGIC THERAPY

Response to ventriculoperitoneal shunting is variable. Some patients (variable depending on series reported) show significant improvement from shunting; however, effectiveness of shunting has never been demonstrated in a randomized-controlled trial. Gait is most likely to improve.

Factors that may predict positive outcome with surgery:

- NPH caused by prior trauma, subarachnoid hemorrhage, or meningitis
- History of mild impairment in cognition <2 yr duration
- Onset of gait abnormality before cognitive decline
- Imaging demonstrates hydrocephalus without sulcal enlargement, including normalized-sized sylvian fissures and cortical sulci, and absent or mild white matter lesions.
- Transepndymal CSF flow visualized on MRI
- Large-volume tap or ELD produces dramatic but temporary relief of symptoms
- High *normal*/opening pressure

Factors that may predict negative outcome with surgery:

- Extensive white matter lesions or diffuse cerebral atrophy on MRI
- Moderate to severe cognitive impairment
- Onset of cognitive impairment before gait disorder
- History of alcohol abuse

### ACUTE GENERAL Rx

Shunting in selected patients

### DISPOSITION

Symptoms of NPH may progress over time. Prompt diagnosis may improve chances for treatment success.

### REFERRAL

To neurologist for initial evaluation, including lumbar puncture, followed by neurosurgeon for shunting in appropriate patients



## PEARLS & CONSIDERATIONS

Each of the cardinal symptoms of NPH is commonly seen in the elderly and occurs in multiple disease processes; therefore differential diagnoses should always be considered carefully.

### CAUTION

Shunt complications, including subdural or intracerebral hematoma, may occur in 30% to 40% of patients.

### SUGGESTED READINGS

Available at [www.expertconsult.com](http://www.expertconsult.com)

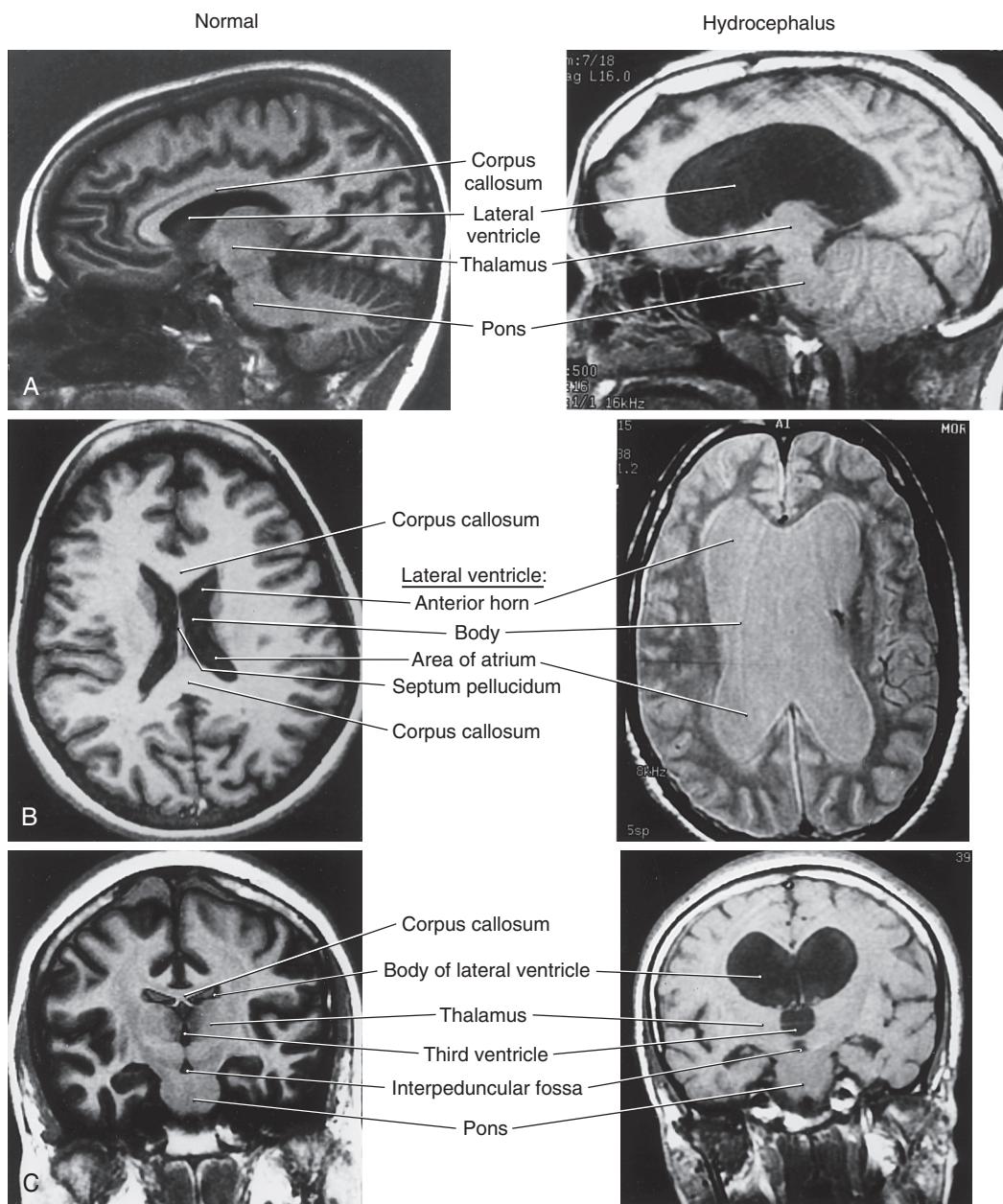
### RELATED CONTENT

Normal Pressure Hydrocephalus (Patient Information)

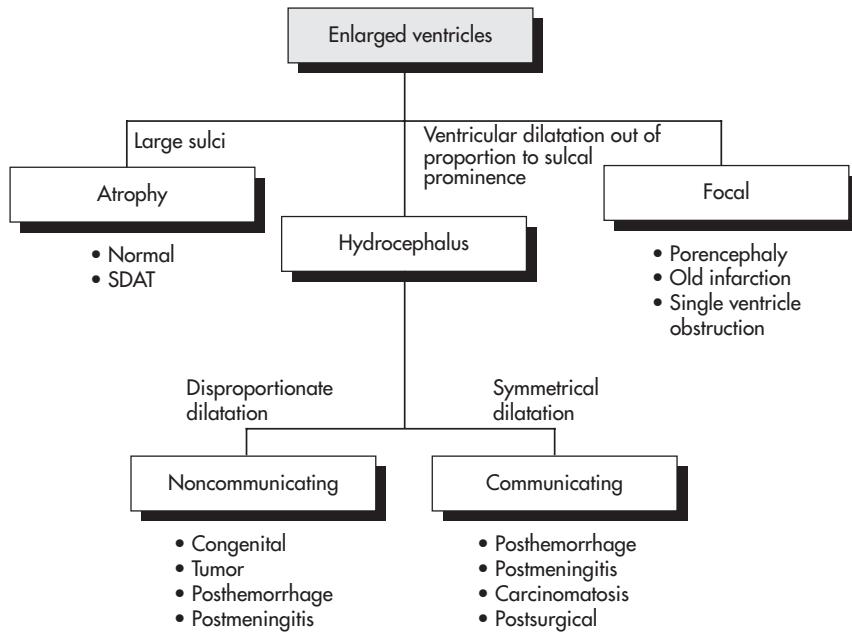
AUTHOR: TAMARA G. FONG, M.D., PH.D.

## Hydrocephalus, Normal Pressure

648.e1



**FIGURE EH1-68** Comparison of normal and hydrocephalic brains in sagittal (A), axial (B), and coronal (C) planes as seen on MR images. (From Haines DE: *Fundamental neuroscience for basic and clinical applications*, ed 3, Philadelphia, 2006, Churchill Livingstone.)



**FIGURE EH1-69 Radiographic differential diagnosis of enlarged ventricles.** (From Weissleder R et al: *Primer of diagnostic imaging*, ed 5, St. Louis, 2011, Mosby.)

## SUGGESTED READINGS

Marmarou A, et al.: The value of supplemental prognostic tests for the preoperative assessment of idiopathic normal-pressure hydrocephalus, *Neurosurgery* 57(suppl 3):17–28, 2005.

Vanneste JA: Diagnosis and management of normal-pressure hydrocephalus, *J Neurol* 247(1):5, 2000.



## BASIC INFORMATION

### DEFINITION

Hydronephrosis is dilation of the renal pyelocalyceal system, most often as a result of impairment of urinary flow.

### SYNOMYS

Hydroureter (dilation of ureter, often seen with hydronephrosis when obstruction is in lower urinary tract)

Urinary tract obstruction

#### ICD-9CM CODES

591 Acquired hydronephrosis

753.2 Congenital hydronephrosis

#### ICD-10CM CODES

N13.30 Unspecified hydronephrosis

Q62.39 Other obstructive defects of renal pelvis and ureter

### EPIDEMIOLOGY & DEMOGRAPHICS

Children usually have congenital malformations, whereas adults tend to have acquired defects as etiologies.

### CLINICAL PRESENTATION

#### HISTORY:

- Pain is caused by distention of collecting system or renal capsule and is more related to the rate of onset than the degree of obstruction. It can vary in location from flank to the lower abdomen to the testes/labia. Pain in the flank occurring only on micturition is highly suggestive of vesicoureteral reflux.
- Anuria can occur with total obstruction of urinary flow (bilateral hydronephrosis, or unilateral if only one kidney is present).
- Polyuria or nocturia can occur with chronic (incomplete) obstruction because of deleterious effects on renal concentrating ability (nephrogenic diabetes insipidus).
- Urinary frequency, hesitancy, poor stream, and postvoid dribbling are all symptoms that can occur with obstruction at or below the bladder (e.g., prostatic hyperplasia).
- Chronic urinary infections can either result from chronic urinary obstruction (organisms favoring growth with stasis of urine) or lead to conditions (e.g., urine pH changes) that favor stone formation and subsequent obstruction.

#### PHYSICAL EXAMINATION

- Hypertension can be caused by increased renin release in acute or subacute obstruction.
- Fever or costovertebral angle (CVA) tenderness can suggest urinary tract infection.
- Palpate bladder to detect if distention is present.
- Rectal examination to evaluate prostate for size and nodularity and also to check rectal sphincter tone.
- Pelvic examination to assess for vaginal anatomy, pelvic mass, or pelvic inflammatory disease.
- Penile examination to rule out meatal stenosis or phimosis.

- Bladder catheterization to assess postvoid residual volume if urinary tract obstruction is considered. Should rule out postrenal obstruction in unexplained acute renal failure.

### ETIOLOGY

#### MECHANICAL IMPAIRMENTS

Congenital:

- Ureteropelvic junction narrowing
- Ureterovesical junction narrowing
- Ureterocele
- Retrocaval ureter
- Bladder neck obstruction
- Urethral valve
- Urethral stricture
- Meatal stenosis

Acquired:

- Intrinsic to urinary tract:
  - Calculi
  - Inflammation
  - Trauma
  - Sloughed papillae
  - Ureteral tumor
  - Blood clots
  - Prostatic hypertrophy or cancer
  - Bladder cancer
  - Urethral stricture
  - Phimosis
- Extrinsic to urinary tract:
  - Gravid uterus
  - Retroperitoneal fibrosis or tumor (e.g., lymphoma)
  - Aortic aneurysm
  - Uterine fibroids
  - Trauma (surgical or nonsurgical)
  - Pelvic inflammatory disease
  - Pelvic malignancies (e.g., prostate, colorectal, cervical, uterine, bladder)

#### FUNCTIONAL IMPAIRMENTS

- Neurogenic bladder (often with adynamic ureter) can occur with spinal cord disease or diabetic neuropathy.
- Pharmacologic agents such as alpha-adrenergic antagonists and anticholinergic drugs can inhibit bladder emptying.
- Vesicoureteral reflux may occur.
- Pregnancy can cause hydroureter and hydronephrosis (on the right more often than left) as early as the second month. Hormonal effects on ureteral tone combine with mechanical factors.

## Dx DIAGNOSIS

### DIFFERENTIAL DIAGNOSIS

- Urinary stones
- Neoplastic disease
- Prostatic hypertrophy
- Neurologic disease
- Urinary reflux
- Urinary tract infection
- Medication effects
- Trauma
- Congenital abnormality of urinary tract

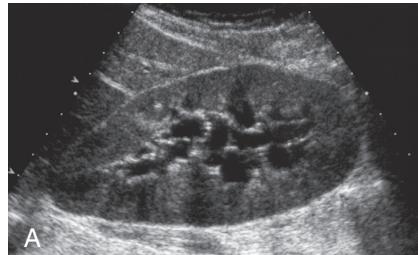
### LABORATORY TESTS

- Serum blood urea nitrogen and creatinine to assess for renal insufficiency (usually implies bilateral obstruction or unilateral obstruction of a solitary kidney).

- Electrolytes may reveal hypernatremia, hyperkalemia, or distal renal tubular acidosis.
- Urinalysis and examination of sediment may reveal white blood cells, red blood cells, or bacteria in the appropriate setting (e.g., infection, stones), but often the sediment is normal in obstructive renal disease.

### IMAGING STUDIES

- Assess kidney and bladder size with ultrasound (Fig. H1-70) as well as contour of collecting system and ureters. Ultrasound is >90% sensitive and specific for hydronephrosis and is noninvasive.
- Abdominal CT scan without IV contrast provides excellent localization of the site of obstruction (Fig. H1-71).
- Magnetic resonance (MR) imaging is an alternative to CT. MR Urography has a similar diagnostic yield to CT but is not yet widely practiced. Poor renal function may preclude the use of gadolinium.
- Once diagnosed, antegrade or retrograde ureterograms can further delineate the point of obstruction.



**FIGURE H1-70** Renal ultrasound study demonstrating hydronephrosis. **A**, Sagittal image. **B**, Transverse image. **C**, Transverse three-dimensional surface-rendered image; arrows indicate the dilated proximal ureter. (From Floege J et al: *Comprehensive clinical nephrology*, ed 4, Philadelphia, 2010, Saunders.)



**FIGURE H1-71** CT scan of the abdomen showing a grossly hydronephrotic kidney on the left. Arrows mark dilated renal pelvis. Dilated loops of small bowel are seen in the right hypochondrium. Sequential sections demonstrated that the ureter was dilated along its length and that there was a pelvic mass, which was responsible for both bowel and left ureteric obstruction. The mass was subsequently shown to be arising from a carcinoma of the colon. (From Johnson RJ, Feehally J: *Comprehensive clinical nephrology*, ed 2, St Louis, 2000, Mosby.)

- Voiding cystourethrogram is helpful in diagnosing vesicoureteral reflux and obstructions of the bladder neck or urethra.
- Diuretic renogram is sometimes used when there is hydronephrosis without apparent obstruction seen on any of the above studies. A loop diuretic is administered prior to a radionuclide scan. If obstruction is present, there will be slowed transit of the radioisotope during the scan, further dilation of the collecting system, and often reproduction of the patient's symptoms.
- A perfusion pressure flow study should be performed in a symptomatic patient with a negative or equivocal diuretic renogram.

## RX TREATMENT

### NONPHARMACOLOGIC THERAPY

- Urgent treatment is required if urinary tract obstruction is associated with urinary tract infection, acute renal failure, or uncontrollable pain.
- Conservative management of calculi with IV fluids, IV antibiotics (if evidence of infection), and aggressive analgesia may be enough to treat acute unilateral urinary tract obstruction

depending on the size (90% of stones <5 mm will pass spontaneously).

- Urethral catheter is adequate to relieve most obstructions at or distal to the bladder, but occasionally a suprapubic catheter will be required (e.g., impassable urethral stricture or urethral injury). Neurogenic bladder may require intermittent clean catheterization if frequent voiding and pharmacologic treatments are ineffective.
- Nephrostomy tube can be placed percutaneously to facilitate urinary drainage.
- Extracorporeal shock wave lithotripsy (ESWL) is used to fragment large stones to facilitate spontaneous passage or subsequent extraction. (Note: ESWL is contraindicated in pregnancy.)
- Nephroscopy is performed for extraction of proximal stones under direct visualization.
- Cystoscopy with ureteroscopy is used to remove distal ureteral stones with a loop or basket with or without fragmentation by ultrasonic or laser lithotripsy.
- Ureteral stents can be used for extrinsic and some intrinsic ureteral obstructions.
- Urethral dilation or internal urethrotomy can be used for urethral strictures.

- Nephrectomy or ureteral diversion may be required in severe cases (e.g., malignancy).
- Ureterovesical reimplantation can be used for reflux disease.
- Transurethral retrograde prostatectomy is used for severe obstruction from benign prostatic hypertrophy.
- IV fluid and electrolyte replacement are needed; the patient must be monitored closely during the postobstructive diuresis (usually lasting several days to a week).

### ACUTE GENERAL Rx

Antibiotics if indicated

### DISPOSITION

Aggressive treatment of infections and early relief of obstruction can usually prevent progressive loss of renal function; however, chronic bilateral obstruction (often from benign prostatic hypertrophy) can lead to chronic renal failure.

### REFERRAL

- Urologist consultation early for diagnostic or therapeutic procedures
- Oncologist if a neoplasm is diagnosed
- Gynecologist if pregnancy or female pelvic anatomy is involved



### PEARLS & CONSIDERATIONS

#### COMMENTS

- Not a primary disorder: an underlying etiology should be sought.

#### PREVENTION

May be achieved through prevention of an underlying potential etiology (e.g., medical or surgical management of benign prostatic hypertrophy before obstruction occurring or medical treatment to avoid formation of renal stones).

#### SUGGESTED READINGS

Available at [www.expertconsult.com](http://www.expertconsult.com)

#### RELATED CONTENT

Hydronephrosis (Patient Information)

AUTHORS: SHEENAGH M. BODKIN, M.D., and PAUL A. PIRRAGLIA, M.D., M.P.H.

## SUGGESTED READINGS

- EAU/AUA Nephrolithiasis Guideline Panel: *Guideline for the management of ureteral calculi*, Baltimore (M.D). American Urological Association Education and Research, Inc., European Association of Urology, 2007. 61 p. [92 references].
- Lameire N et al.: Acute renal failure, *Lancet* 365:417–430, 2005.
- Licurso A, Kim MC, Dziura J et al.: Renal ultrasonography in the evaluation of acute kidney injury, *Arch Intern Med* 170(21):1900–1907, 2010.



## BASIC INFORMATION

### DEFINITION

*Hypercholesterolemia* refers to a blood cholesterol measurement  $\geq 200$  mg/dl.

### SYNOMYS

Hypercholesterolemia  
Dyslipidemia  
Type II familial hyperlipoproteinemia

#### ICD-9CM CODES

272.0 Pure hypercholesterolemia

#### ICD-10CM CODES

E78.0 Pure hypercholesterolemia

### EPIDEMIOLOGY & DEMOGRAPHICS

- Over 105 million (37%) adults in the U.S. have total blood cholesterol levels higher than 200 mg/dl. Of this group, more than 36 million adults have extremely high-risk cholesterol levels over 240 mg/dl (13%).
- For men over the age of 20 years, approximately 48% of white men, 45% of black men, and 50% of Hispanic men have high blood cholesterol.
- For women over the age of 20, approximately 50% of white women, 42% of black women, and 50% of Hispanic women have hypercholesterolemia.
- Prevalence of hypercholesterolemia increases with increasing age.
- According to NHANES data for 2009-2010, about 47% of adults had at least one of three risk factors for cardiovascular disease—uncontrolled high blood pressure, uncontrolled high levels of low-density lipoproteins (LDL) cholesterol, or current smoking.

### PHYSICAL FINDINGS & CLINICAL PRESENTATION

- A detailed medication history should be performed because some medications may affect lipid levels (e.g., thiazides, corticosteroids, beta-blockers, and estrogens).
- The physical examination should include measurements of BMI and BP, thyroid and liver assessments, and examining peripheral pulses including carotids for bruits.
- Physical findings, particularly in the familial forms may include
  - Tendon xanthomas
  - Xanthelasma
  - Arcus cornea
  - Arterial bruits (young adulthood)

### ETIOLOGY

Primary:

- Genetics
- Obesity
- Dietary intake

Secondary:

- Hypothyroidism
- Diabetes mellitus
- Nephrotic syndrome
- Obstructive liver disease: Hepatoma, extrahepatic biliary obstruction, primary biliary cirrhosis

- Alcohol or tobacco use
- Dysgammaglobulinemia (multiple myeloma, SLE)
- Drugs: Oral contraceptives, progesterone, corticosteroids, thiazide diuretics,  $\beta$ -blockers, androgenic steroids, retinoic acid derivatives, protease inhibitors

## Dx DIAGNOSIS

### DIFFERENTIAL DIAGNOSIS

- Always consider underlying secondary causes for the elevated cholesterol.
- Patients with very high LDL cholesterol usually have genetic forms of hypercholesterolemia (see *Hyperlipoproteinemia, Primary*). Early detection of these cases and family testing to identify similarly affected relatives is important.
- Metabolic syndrome:
  - A constellation of lipid and nonlipid risk factors of a metabolic origin
  - Diagnosed when three or more of the following are present: abdominal obesity (waist circumference  $>40$  in in men and  $>35$  in women); fasting triglycerides  $>150$  mg/dl; HDL  $<40$  mg/dl in males and  $<50$  mg/dl in females; systolic BP  $>130$  mmHg and diastolic BP  $>85$  mmHg; fasting glucose  $>110$  mg/dl

### WHO SHOULD BE SCREENED

- AACE recommends screening of patients  $>20$  yr of age for elevated cholesterol every 5 yr, males  $>45$  yr and females  $>55$  yr of age every 1-2 yr, and  $>65$  yr of age every yr up to 75 yr of age regardless of CAD risk status. Patients above 75 yr of age with multiple CAD risk factors should still continue to get screened annually.
- The USPSTF supports routine screening for men aged  $>35$  yr and women aged  $>45$  yr by measurement of nonfasting total and HDL cholesterol alone.
- In 2010, the USPSTF recommended routine screening for overweight and obesity in persons aged  $<20$  yr.
- In 2011, ACC/AHA recommended screening for hypertriglyceridemia by a nonfasting measurement. A nonfasting level of  $<200$  mg/dl is commensurate with an optimal level of  $<100$  mg/dl and no further testing is required. However, a nonfasting level of  $>200$  mg/dl warrants further testing with a fasting lipid profile.
- Maintenance of a healthy weight
- Avoidance of tobacco products
- Counseling on CAD risk factors (Table H1-38)
- Plant-based diets (including stanol-containing margarines, oat bran, and nuts) have shown effectiveness in controlling lipids.

**TABLE H1-38** Risk Factors for Heart Disease

- Cigarette smoking
- Hypertension (BP  $\leq 140/90$  mm Hg or on medications)
- Low HDL cholesterol ( $<40$  mg/dl)\*
- Family history of premature CHD ( $<55$  yr in first-degree male relative or  $<65$  yr in first-degree female relative)
- Age (men  $\geq 45$  yr, women  $\geq 55$  yr)

\*HDL cholesterol  $>60$  mg/dl counts as a negative risk factor; its presence removes one risk factor from the total count.

**TABLE H1-39** Atherosclerotic Cardiovascular Disease

- Coronary heart disease: acute coronary syndromes, history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization
- Stroke or transient ischemic attack
- Peripheral arterial disease
- Polyunsaturated fat up to 10% of total calories
- Monounsaturated fat up to 20% of total calories
- Saturated fats  $<7\%$  of total calories
- Carbohydrate 50% to 60% of total calories
- Protein 15% of total calories
- No more than 200 mg/day of cholesterol
- Fiber 20 to 30 g/day
- Increased physical activity: encourage 30 min of moderately intense physical activity, four to six times a week (e.g., brisk walking, riding stationary bike, water aerobics)
- Maintenance of a healthy weight
- Avoidance of tobacco products
- Counseling on CAD risk factors (Table H1-38)
- Plant-based diets (including stanol-containing margarines, oat bran, and nuts) have shown effectiveness in controlling lipids.

### ACUTE GENERAL Rx

No acute treatment needed

### CHRONIC Rx

- The current guidelines represent a substantial departure from previous recommendations, which were based on LDL levels.
- The new guidelines identify **four high-risk groups** that benefit from statin therapy: **Patients with clinical ASCVD (atherosclerotic cardiovascular disease) (Table H1-39)**
- LDL  $\geq 190$  mg/dl
- DM aged 40-75 years and LDL 70-189 mg/dl
- Ten-year risk for ASCVD  $\geq 7.5\%$  and LDL 70-189 mg/dl
- The 10-year risk of ASCVD is calculated with the risk calculator available at <http://my.ameicanheart.org/cvriskcalculator>
- ASCVD events are reduced by using the maximum tolerated statin intensity in the above groups shown to benefit the most (Tables H1-40 and H1-41).

**TABLE H1-40** Statin Intensity Therapies

High Intensity (Decrease LDL-C ≥50%)	Moderate Intensity (Decrease LDL-C 30%-49%)
Atorvastatin 40-80 mg	Atorvastatin 10-20 mg
Rosuvastatin 20-40 mg	Rosuvastatin 5-10 mg
—	Simvastatin 20-40 mg
—	Pravastatin 40-80 mg
—	Lovastatin 40 mg
—	Fluvastatin XL 80 mg
—	Fluvastatin 40 mg bid
—	Pitavastatin 2-4 mg

LDL-C, Low-density lipoprotein cholesterol.

From Stone N et al: 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, *J Am Coll Cardiol* 63(25 Pt. B):2889, 2014.

**TABLE H1-41** Statin Benefit Groups and Recommended Therapy

Statin Benefit Group	High Intensity	Moderate Intensity	Additional Testing
Clinical ASCVD	Yes	Consider <sup>†</sup>	None
Primary LDL-C >190 mg/dl	Yes	Consider <sup>†</sup>	None
Diabetes without ASCVD and 10-year risk ≥7.5%*	Yes	Consider <sup>†</sup>	None
Diabetes without ASCVD and 10-year risk <7.5%*	Consider <sup>‡</sup>	Yes	Case-by-case
Primary prevention and 10-year risk ≥7.5%*	Consider <sup>‡</sup>	Yes	Case-by-case
Primary prevention and 10-year risk <7.5%*	Consider <sup>‡</sup>	Consider <sup>‡</sup>	Case-by-case

ASCVD, Atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

\*Based on Pooled Cohort Risk Equations.

<sup>†</sup>If age >75 years or not candidate for high intensity.

<sup>‡</sup>If abnormal high-sensitivity C-reactive protein, coronary artery calcium, ankle-brachial index, lifetime risk.

From Boyden TF et al: Implementing new guidelines in the management of blood cholesterol, *Am J Med* 127:705, 2014.

- Additional factors such as CRP >2 mg/L, primary LDL >160, genetic hyperlipidemias, family history of premature CHD, ABI <0.9, and CAD score >300 Agatston units may be used in patients who are not in one of four statin benefit groups and for whom a decision to initiate statin therapy is otherwise unclear.
- Percent reduction in LDL cholesterol is used as a guide to compliance and adherence to therapy but is not considered a treatment goal.
- Moderate-intensity statin therapy should be continued for individuals >75 years of age for secondary prevention. However, factors such as comorbidities, safety, and priorities of care should be considered before initiating statins for primary prevention of ASCVD.
- Adherence to lifestyle and to statin therapy should be reiterated with patients before the addition of a nonstatin drug.
- Nonstatin therapies do not provide acceptable ASCVD risk reduction benefits compared with their potential adverse effects in ASCVD prevention.
- High-risk patients with a suboptimal response to statins who are unable to tolerate a recommended intensity or who are completely statin intolerant may benefit from the addition of a nonstatin cholesterol-lowering agent.
- The management of metabolic syndrome includes weight reduction, increased physical activity, and treatment of hypertension, elevated triglycerides, and low HDL cholesterol.
- According to recent studies, each 40 mg/dl reduction in LDL cholesterol by statin therapy confers a 20% reduction in ASCVD. In other words, a relative risk reduction of 30% in ASCVD by moderate-intensity therapy and 45% by high-intensity therapy has been approximated.

#### DISPOSITION AND FOLLOW-UP

- Baseline LFT testing should be done before initiation of statin therapy and as clinically indicated thereafter.
- CK level monitoring is not recommended unless a patient reports muscle weakness or myalgias.
- Statin therapy should be monitored by repeating a lipid profile within 4-12 weeks after initiation of therapy.
- Counseling about behavioral lifestyle changes and risk factors for CHD should be provided at every follow-up visit.
- Adverse effects of statin-associated diabetes varies by statin intensity: 1 excess case of diabetes per 1000 treated individuals with moderate-intensity statin and 3 excess

cases of diabetes per 1000 treated individuals with high-intensity statin per year has been reported. Myopathy and hemorrhagic stroke incidence is around 1 excess case per 10,000 treated individuals.

- Per new guidelines, those who develop diabetes during statin therapy should be advised to continue it to reduce their risk of ASCVD events and should adhere to a heart-healthy diet, engage in physical activity, cease tobacco use, and maintain a healthy body weight (Table H1-42).

#### REFERRAL

Patients with rare lipid disorders, hyperlipoproteinemias, patients resistant to treatment, on complex regimens, and with evidence of disease progression despite treatment should be referred to a lipid specialist.



#### PEARLS & CONSIDERATIONS

##### COMMENTS

- The American Academy of Pediatrics (AAP) guideline (*Pediatrics* 122:198, 2008) recommends consideration toward pharmacologic treatment for children with LDL >190 mg/dl or >160 mg/dl if other risk factors are present.
- HDL cholesterol efflux capacity refers to the ability of HDL to accept cholesterol from macrophages, which is a key step in reverse cholesterol transport. It is inversely associated with the incidence of cardiovascular events and may be a useful biomarker when added to traditional risk factors.



#### EVIDENCE

Available at [www.expertconsult.com](http://www.expertconsult.com)

#### SUGGESTED READINGS

Available at [www.expertconsult.com](http://www.expertconsult.com)

#### RELATED CONTENT

High Cholesterol (Patient Information)  
Hyperlipoproteinemia, Primary (Related Key Topic)

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