# Outpatient and Primary Care Medicine

New NMS guidelines

2005 Edition

Paul D. Chan, MD
David M. Thomas, MD
Eric W. McKinley, MD
Elizabeth K. Stanford, MD

***Current Clinical Strategies Publishing***

***www.ccspublishing.com/ccs***

## Digital Book and Updates

Purchasers of this book may download the digital book and updates for Palm, Pocket PC, Windows and Macintosh. The digital books can be downloaded at the Current Clinical Strategies Publishing Internet site:

***www.ccspublishing.com/ccs/op.htm***



**Current Clinical Strategies Publishing**
27071 Cabot Road
Laguna Hills, California 92653-7011
Phone: 800-331-8227
Fax: 800-965-9420
Internet: www.ccspublishing.com/ccs
E-mail: info@ccspublishing.com

Printed in USA ISBN 1929622-45-7

# Cardiovascular Disorders

## Stable Angina Pectoris

Angina pectoris is a symptom complex caused by myocardial ischemia. Stable angina refers to chest discomfort that occurs predictably and reproducibly at a certain level of exertion and is relieved with rest or nitroglycerin. Unstable angina includes new onset of chest pain, progressing effort angina, rest angina, post-myocardial infarction angina, and angina after revascularization.

**I.Clinical evaluation**

**A.Important points include the following:**

**1.**History of previous heart disease

**2.**Possible non-atheromatous causes of angina (eg, aortic stenosis)

**3.**Symptoms of systemic atherosclerosis (eg, claudication)

**4.**Severity and pattern of symptoms of angina

**5.**Risk factors for coronary heart disease, include smoking, inappropriate activity level, stress, hyperlipidemia, obesity, hypertension, and diabetes mellitus.

**B.Physical examination** should include a cardiovascular examination, evaluation for hyperlipidemia, hypertension, peripheral vascular disease, congestive heart failure, anemia, and thyroid disease.

**C.Laboratory studies** should include an electrocardiogram and a fasting lipid profile. Further studies may include chest films, hemoglobin, and tests for diabetes, thyroid function, and renal function.

**D.Exercise electrocardiography.** An exercise test should be obtained for prognostic information.

**1.**Sensitivity of exercise electrocardiography may be reduced for patients unable to reach the level of exercise required for near maximal effort, such as:

**a.**Patients taking beta blockers

**b.**Patients in whom fatigue, dyspnea, or claudication symptoms develop

**c.**Patients who cannot perform leg exercises

**2.**Reduced specificity may be seen in patients with abnormalities on baseline electrocardiograms, such as those taking digoxin or with left ventricular hypertrophy or left bundle branch block.

**E.Noninvasive imaging,** such as myocardial perfusion scintigraphy or stress echocardiography, may be indicated in patients unable to complete exercise electrocardiography.

**II.Medical treatment of stable angina pectoris**

**A.Nitrates**

**1.Nitrates** are a first-line therapy for the treatment of acute anginal symptoms. While they act as venodilators, coronary vasodilators, and modest arteriolar dilators, the primary antiischemic effect of nitrates is to decrease myocardial oxygen demand by producing systemic vasodilation more than coronary vasodilation.

**2.**In combination with beta blockers or calcium channel blockers, nitrates produce greater antianginal and antiischemic effects. There is no difference in efficacy among preparations.

**3.Sublingual nitroglycerin**

**a.**Sublingual nitroglycerin (Nitrostat) is the therapy of choice for acute anginal episodes and prophylactically for activities known to elicit angina.

**b.**The initial dose is 0.3 mg. A second dose can be taken if symptoms persist after three to five minutes.

**4.Chronic nitrate therapy**

**a.**Chronic nitrate therapy, in the form of an oral or transdermal preparation (isosorbide dinitrate, isosorbide mononitrate, or transdermal nitroglycerin) can prevent or reduce the frequency of recurrent anginal episodes and improve exercise tolerance. Chronic nitrate therapy is a second-line antianginal therapy.

**b.Isosorbide dinitrate (ISDN, Isordil SR, Dilatrate-SR, Isordil Tembids)** dosing begins with a dose of 10 mg at 8 AM, 1 PM, and 6 PM, which results in a 14 hour nitrate dose-free interval. The dose is increased to 40 mg three times daily as needed. Alternatively, isosorbide dinitrate can be taken twice daily at 8 AM and 4 PM.

**c.**The extended release preparation of isosorbide mononitrate (Imdur), which is administered once per day, may be preferable to improve compliance. The starting dose is 30 mg once daily and can be titrated to 120 mg once daily as needed. Some patients may develop nocturnal or rebound angina, which requires twice daily dosing or additional antianginal therapy.

**d.Transdermal nitroglycerin (Transderm-Nitro).** Use of a transdermal patch is convenient. Since most patients have angina with activity, that the patch should be applied at 8 AM and removed at 8 PM. The occasional patient with significant nocturnal angina can be treated with a patch-on period from 8 PM to 8 AM. The initial dose is 0.2 mg per hour; the dose can be increased to 0.8 mg per hour as needed.

**Nitrate Preparations**

| Preparation | Route of Administration | Dosage |
|---|---|---|
| Nitroglycerine (Nitrostat) | Sublingual tab | 0.15-0.9 mg |
| Nitroglycerine (Nitrolingual) | Sublingual spray | 0.4 mg |
| Nitroglycerine (Transderm-Nitro) | Transdermal | 0.2-0.8 mg/h |
| Isosorbide dinitrate (Isordil SR) | Oral | 10-40 mg tid |
| Isosorbide mononitrate (ISMN) | Oral | 20-40 mg bid |
| ISMN, extended release (Imdur) | Oral | 30-120 mg once daily |

**e.Side effects** associated with nitrate use are headache, lightheadedness, and flushing.

**B.Beta blockers**

**1.**Beta blockers relieve anginal symptoms by inhibiting sympathetic stimulation of the heart, reducing heart rate and contractility. A beta-blocker should be initiated in patients with more frequent angina unless contraindicated. Beta blockers should be given to virtually all patients who have had a prior MI or who have stable heart failure.

**2.Choice of agents**

**a.**Lower doses of the cardioselective beta blockers (atenolol and metoprolol) have the advantage of blocking beta-1-receptor mediated stimulation of the heart with lesser inhibition of the peripheral vasodilation and bronchodilation induced by the beta-2 receptors. A long acting cardioselective agent (atenolol or metoprolol) is preferred for the treatment of stable angina. There are no major advantages of a nonselective agent, other than the low cost of propranolol, and there are disadvantages in obstructive lung disease, asthma, peripheral vascular disease, diabetes, and depression.

**b.Atenolol (Tenormin)** starting dose is 25 mg once daily which can be increased as tolerated to a maximum of 200 mg once a day until the resting heart rate is 50 to 60 beats/min and does not exceed 100 beats/min with ordinary activity.

**c.Metoprolol (Lopressor)** starting dose is 25 mg BID, which can be increased to 200 mg BID as tolerated. Extended release metoprolol (Toprol XL), given once per day, can be substituted once an effective dose has been established; 50-200 mg qd.

**d.**Beta blockers are generally well tolerated and extremely effective in reducing anginal episodes and improving exercise tolerance. In addition, beta blockers are the only antianginal drugs proven to prevent reinfarction and to improve survival in patients who have sustained an MI.

**Adverse Effects of Beta-blockers**

Bradycardia, decreased contractility, AV node conduction delay
Bronchoconstriction can be induced by nonselective agents and high doses of cardioselective agents.
Worsening of symptoms of peripheral vascular disease or Raynaud's phenomenon.
Fatigue may be due to the reduction in cardiac output or to direct effects on the central nervous system.
Central side effects include depression, nightmares, insomnia, and hallucinations.
Impotence is often a problem.

**Beta-blockers**

| Class | Drug name | Starting dose | Maximal dose |
|---|---|---|---|
| Cardioselective | Atenolol (Tenormin) | 25 mg QD | 100 mg QD |
| Cardioselective | Metoprolol (Lopressor) | 25 mg BID | 100 mg BID |
| | Metoprolol extended release (Toprol XL) | 50 mg qd | 200 mg qd |
| Nonselective | Nadolol (Corgard) | 25 mg QD | 240 mg QD |
| Nonselective | Propranolol (Inderal) | 40 mg BID | 120 mg BID |
| Intrinsic sympathomimetic | Pindolol (Visken) | 5 mg BID | 30 mg BID |
| Alpha blocker | Labetalol (Normodyne) | 100 mg BID | 600 mg BID |

**3.Achieving adequate beta blockade.** Goals when titrating the dose include resting heart rate between 50 and 60 beats/min.

**4.Side effects.** The most frequent side effects associated with beta blockers include bradycardia, conduction disturbances, bronchoconstriction, worsening of symptoms of peripheral vascular disease, fatigue, central nervous system side effects, and impotency. Beta blockers should be used with caution in obstructive airways disease or peripheral vascular disease and, initially at very low doses in heart failure.

**C.Calcium channel blockers**

**1.**Calcium channel blockers prevent calcium entry into vascular smooth muscle cells and myocytes, which leads to coronary and peripheral vasodilatation, decreased atrioventricular (AV) conduction, and reduced contractility.

**2.Choice of agent**

**a.**Verapamil is a negative inotrope that also slows sinus rate and is a much less potent vasodilator than the dihydropyridines.

**b.**The dihydropyridines (eg, nifedipine, nicardipine, felodipine, amlodipine) are potent vasodilators with less effect on contractility and AV conduction.

**c.**Diltiazem is a modest negative inotropic and chronotropic agent and vasodilator and has intermediate effects between the dihydropyridines and verapamil.

**d.**If a calcium channel blocker is used, long-acting diltiazem or verapamil or a second generation dihydropyridine (amlodipine or felodipine) should be selected. Short-acting dihydropyridines, especially nifedipine, should be avoided because of increased mortality after an MI and an increase in acute MI in hypertensive patients.

**3.When to use**. A calcium channel blocker should be used in combination with a beta blocker when initial treatment with a beta blocker is not successful. They may be a substitute for a beta blocker when beta blockers are contraindicated or cause side effects.

**4.Side effects** include symptomatic bradycardia, heart block, worsening heart failure, constipation, flushing, headache, dizziness, and pedal edema.

**D.ACE inhibitors**. Most patients with angina will be treated with an ACE inhibitor because of a previous infarction, left ventricular dysfunction, or hypertension.

**E.General and lifestyle measures**

**1.Aspirin.** In the absence of a contraindication, all patients should be treated with aspirin (81 mg/day [one baby aspirin per day] to 325 mg/day). Clopidogrel (Plavix), 75 mg qd, is an alternative when aspirin is contraindicated.

**2.Risk factor reduction** should include treatment of hypertension, cessation of smoking, lipid lowering, weight reduction, and glycemic control in diabetics. Almost every patient with CHD who has a serum LDL-cholesterol concentration above 100 mg/dL should be treated with a statin, such as atorvastatin (Lipitor)10-40 mg PO qhs.

**F.Exercise testing**

**1.**An exercise ECG test should be obtained in all patients with stable angina to evaluate the efficacy of the antiischemic program and for prognostic information.

**2.**Initial stress test options include exercise ECG, exercise with perfusion imaging, pharmacologic stress testing with imaging (echocardiography or myocardial perfusion scan). A standard exercise ECG is preferred as the initial test in patients with a normal resting ECG who are able to exercise and are not taking digoxin.

**G.Coronary angiography.** There are two primary indications for coronary angiography followed by revascularization of appropriate lesions:

**1.**Angina which significantly interferes with a patient's lifestyle despite maximal tolerable medical therapy.

**2.**The presence of high-risk criteria on noninvasive testing would indicate improved prognosis with revascularization.

**H.Coronary revascularization.** Despite effective medical therapy, a significant number of patients are candidates for PCI or surgical revascularization with CABG. Revascularization is also performed when the patient is active and prefers revascularization for improved quality of life compared to medical therapy.

**References:** See page 255.

# Heart Failure Caused by Systolic Dysfunction

Approximately 5 million Americans have heart failure, and an additional 400,000 develop heart failure annually. Coronary artery disease producing ischemic cardiomyopathy is the most frequent cause of left ventricular systolic dysfunction.

## I.Diagnosis

**A.**Left ventricular systolic dysfunction is defined as an ejection fraction of less than 40 percent. The ejection fraction should be measured to determine whether the symptoms are due to systolic dysfunction or another cause.

**B.Presenting Signs and Symptoms**

**1.**Heart failure often presents initially as dyspnea with exertion or recumbency. Patients also commonly have dependent edema, rapid fatigue, cough and early satiety. Arrhythmias causing palpitations, dizziness or aborted sudden death may also be initial manifestations.

**Classification of Patients with Heart Failure Caused by Left Ventricular Dysfunction**

| New classification based on symptoms | Corresponding NYHA class |
|---|---|
| Asymptomatic | NYHA class I |
| Symptomatic | NYHA class II/III |
| Symptomatic with recent history of dyspnea at rest | NYHA class IIIb |
| Symptomatic with dyspnea at rest | NYHA class IV |

**Precipitants of Congestive Heart Failure**

- Myocardial ischemia or infarction
- Atrial fibrillation
- Worsening valvular disease
- Pulmonary embolism
- Hypoxia
- Severe, uncontrolled hypertension
- Thyroid disease
- Pregnancy
- Anemia
- Infection
- Tachycardia or bradycardia
- Alcohol abuse
- Medication or dietary noncompliance

**C.Diagnostic Studies**

**1.Electrocardiography.** Standard 12-lead electrocardiography should be used to determine whether ischemic heart disease or rhythm abnormalities are present.

**2.Transthoracic echocardiography** confirms systolic dysfunction by measurement of the left ventricular ejection fraction and provides information about ventricular function, chamber size and shape, wall thickness and valvular function.

**3.Exercise stress testing** is useful for evaluating active and significant concomitant coronary artery disease.

**4.Other Studies.** Serum levels of atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) are elevated in patients with heart failure. ANP and BNP levels may predict prognosis and are used to monitor patients with heart failure.

**Laboratory Workup for Suspected Heart Failure**

- Blood urea nitrogen
- Cardiac enzymes (CK-MB, troponin)
- Complete blood cell count
- Creatinine
- Electrolytes
- Liver function tests
- Magnesium
- Thyroid-stimulating hormone
- Urinalysis
- Echocardiogram
- Electrocardiography
- Impedance cardiography
- Atrial natriuretic peptide (ANP)
- Brain natriuretic peptide (BNP)

## II.Treatment of heart failure

**A.Lifestyle modification**

**1.Cessation of smoking** and avoidance of more than moderate alcohol ingestion.

**2.Salt restriction** to 2 to 3 g of sodium per day to minimize fluid accumulation.

**3.Water restriction** in patients who are also hyponatremic.

**4.Weight reduction** in obese subjects.

**5.Cardiac rehabilitation** program for all stable patients.

**B.**Improvement in symptoms can be achieved by digoxin, diuretics, beta-blockers, ACE inhibitors, and ARBs. Prolongation of survival has been documented with ACE inhibitors, beta-blockers, and, in advanced disease, spironolactone. Initial management with triple therapy

(digoxin, ACE inhibitor, and diuretics) is recommended in agreement with the ACC/AHA task force guidelines.

**C.ACE inhibitors and other vasodilators.** All patients with asymptomatic or symptomatic left ventricular dysfunction should be started on an ACE inhibitor. Beginning therapy with low doses (eg, 2.5 mg of enalapril BID or 6.25 mg of captopril TID) will reduce the likelihood of hypotension. If initial therapy is tolerated, the dose is then gradually increased to a maintenance dose of 10 mg BID of enalapril, 50 mg TID of captopril, or up to 40 mg/day of lisinopril or quinapril. Angiotensin II receptor blockers appear to be as effective as ACE inhibitors and are primarily given to patients who cannot tolerate ACE inhibitors, generally due to chronic cough or angioedema.

**D.Beta-blockers.** Beta-blockers, particularly carvedilol, metoprolol, bisoprolol, improve survival in patients with New York Heart Association (NYHA) class II to III HF and probably in class IV HF. Carvedilol, metoprolol, or bisoprolol is recommended for symptomatic HF, unless contraindicated.

**1.Relative contraindications to beta-blockers:**

**a.**Heart rate <60 bpm.
**b.**Systolic arterial pressure <100 mm Hg.
**c.**Signs of peripheral hypoperfusion.
**d.**PR interval >0.24 sec.
**e.**Second- or third-degree atrioventricular block.
**f.**Severe chronic obstructive pulmonary disease.
**g.**History of asthma.
**h.**Severe peripheral vascular disease.

**2.**In the absence of a contraindication, carvedilol, metoprolol, or bisoprolol should be offered to patients with NYHA class II, III and IV HF due to systolic dysfunction.

**3.Initiation of therapy.** Therapy should be begun in very low doses and the dose doubled (every two to three weeks) until the target dose is reached or symptoms become limiting.

**a.Carvedilol (Coreg)**, initial dose 3.125 mg BID; target dose 25 to 50 mg BID.
**b.Metoprolol (Lopressor)**, initial dose 6.25 mg BID; target dose 50 to 75 mg BID, and for extended-release metoprolol (Toprol XL), initial dose 12.5 or 25 mg daily, and target dose 200 mg/day.
**c.Bisoprolol (Zebeta)**, initial dose 1.25 mg QD; target dose 5 to 10 mg QD.

**E.Digoxin (Lanoxin)** is given to patients with HF and systolic dysfunction to control fatigue, dyspnea, and exercise intolerance and, in patients with atrial fibrillation, to control the ventricular rate. Digoxin therapy is associated with a significant reduction in hospitalization but has no effect on survival.

**1.**Digoxin should be started in patients with left ventricular systolic dysfunction and NYHA functional class II, III and IV heart failure. The usual daily dose is 0.125 to 0.25 mg, based upon renal function. The serum digoxin is maintained between 0.7 to 1.2 ng/mL.

**2.**Digoxin is not indicated as primary therapy for the stabilization of patients with acutely decompensated HF. Such patients should first receive appropriate treatment for HF, usually with intravenous medications.

**F.Diuretics**

**1.**A loop diuretic should be given to control pulmonary and/or peripheral edema. The usual starting dose in outpatients with HF is 20 to 40 mg of furosemide (Lasix). Subsequent dosing is determined with goal weight reduction of 0.5 to 1.0 kg/day. If a patient does not respond, the dose should be increased. In patients with a relatively normal glomerular filtration rate, the maximum single doses are 40 to 80 mg of furosemide.

**G.Spironolactone**. A low dose of spironolactone (25 to 50 mg/day) is recommended in patients with symptoms at rest (despite therapy with the above medications), a serum creatinine concentration less than 2.5 mg/dL (221 µmol/L), and a serum potassium less than 5 meq/L.

**Treatment Classification of Patients with Heart Failure Caused by Left Ventricular Systolic Dysfunction**

| Symptoms | Pharmacology |
|---|---|
| Asymptomatic | ACE inhibitor<br>Beta blocker |
| Symptomatic | ACE inhibitor<br>Beta blocker<br>Diuretic<br>If symptoms persist: digoxin (Lanoxin) |
| Symptomatic with recent history of dyspnea at rest | Diuretic<br>ACE inhibitor<br>Spironolactone (Aldactone)<br>Beta blocker<br>Digoxin |
| Symptomatic with dyspnea at rest | Diuretic<br>ACE inhibitor<br>Spironolactone (Aldactone)<br>Digoxin |

| Dosages of Primary Drugs Used in the Treatment of Heart Failure | | |
|---|---|---|
| **Drug** | **Starting Dosage** | **Target Dosage** |
| **Drugs that decrease mortality and improve symptoms** | | |
| **ACE inhibitors** | | |
| Captopril (Capoten) | 6.25 mg three times daily (one-half tablet) | 12.5 to 50 mg three times daily |
| Enalapril (Vasotec) | 2.5 mg twice daily | 10 mg twice daily |
| Lisinopril (Zestril) | 5 mg daily | 10 to 20 mg daily |
| Ramipril (Altace) | 1.25 mg twice daily | 5 mg twice daily |
| Trandolapril (Mavik) | 1 mg daily | 4 mg daily |
| **Aldosterone antagonist** | | |
| Spironolactone (Aldactone) | 25 mg daily | 25 mg daily |
| **Beta blockers** | | |
| Bisoprolol (Zebeta) | 1.25 mg daily (one-fourth tablet) | 10 mg daily |
| Carvedilol (Coreg) | 3.125 mg twice daily | 25 to 50 mg twice daily |
| Metoprolol tartrate (Lopressor) | 12.5 mg twice daily (one-fourth tablet) | 50 to 75 mg twice daily |
| Metoprolol succinate (Toprol-XL) | 12.5 mg daily (one-half tablet) | 200 mg daily |
| **Drugs that treat symptoms** | | |
| **Thiazide diuretics** | | |
| Hydrochlorothiazide (Esidrex) | 25 mg daily | 25 to 100 mg daily |
| Metolazone (Zaroxolyn) | 2.5 mg daily | 2.5 to 10 mg daily |
| **Loop diuretics** | | |
| Bumetanide (Bumex) | 1 mg daily | 1 to 10 mg once to three times daily |
| Ethacrynic acid (Edecrin) | 25 mg daily | 25 to 200 mg once or twice daily |
| Furosemide (Lasix) | 40mg daily | 40 to 400 mg once to three times daily |
| Torsemide (Demadex) | 20 mg daily | 20 to 200 mg once or twice daily |
| **Inotrope** | | |
| Digoxin (Lanoxin) | 0.125 mg daily | 0.125 to 0.375 mg daily |

**Angiotensin Receptor Blockers for Heart Failure**

Candesartan (Atacand) – start 4-8 mg qd bid, target 8-16 mg qd-bid
Eprosartan (Teveten) – start 400-800 mg qd, target 800 mg/d
Irbesartan (Avapro) – start 75-150 mg qd, target 150-300 mg qd
Losartan (Cozaar) – start 25-50 mg qd, target 50 mg bid
Valsartan (Diovan) – start 80 mg qd, target 160-320 mg qd

**H.Management of refractory heart failure**

**1.Inotropic agents other than digoxin.** Patients with decompensated HF are often treated with an intravenous infusion of a positive inotropic agent, such as dobutamine, dopamine, milrinone, or amrinone.

**2.**Symptomatic improvement has been demonstrated in patients after treatment with a continuous infusion of dobutamine (at a rate of 5 to 7.5 µg/kg per min) for three to five days. The benefit can last for 30 days or more. Use of intravenous dobutamine is limited to the inpatient management of patients with severe decompensated heart failure.

**3.Natriuretic peptides**

**a.**Atrial and brain natriuretic peptides regulate cardiovascular homeostasis and fluid volume.

**b.Nesiritide (Natrecor)** is structurally similar to atrial natriuretic peptide. It has natriuretic, diuretic, vasodilatory, smooth-muscle relaxant properties, and inhibits the renin-angiotensin system. Nesiritide is indicated for the treatment of moderate-to-severe heart failure. The initial dose of is 0.015 mcg/kg/min IV infusion, max 0.03 mcg/kg/min.

**4.Pacemakers.** Indications for pacemakers in patients with HF include symptomatic bradycardia, chronic AF, or AV nodal ablation. Patients with refractory HF and severe symptoms may benefit from long-term dual-chamber pacing.

**5.Hemofiltration.** Extracorporeal ultrafiltration via hemofiltration removes intravascular fluid; it is an effective treatment for patients with refractory HF.

**6.Mechanical circulatory support.** Circulatory assist devices are used for refractory HF. There are three major types of devices:

**a.**Counterpulsation devices (intraaortic balloon pump and noninvasive counterpulsation).

**b.**Cardiopulmonary assist devices.

**c.**Left ventricular assist devices.

**7.Indications for cardiac transplantation**

**a.**Repeated hospitalizations for HF.

**b.**Escalation in the intensity of medical therapy.

**c.**A reproducible peak oxygen of less than 14 mL/kg per min.
**d.**Other absolute indications for cardiac transplantation, recommended:
Refractory cardiogenic shock.
Continued dependence on intravenous inotropes.
Severe symptoms of ischemia that limit routine activity and are not amenable to revascularization or recurrent unstable angina not amenable to other intervention.
Recurrent symptomatic ventricular arrhythmias refractory to all therapies.

**Treatment of Acute Heart Failure/Pulmonary Edema**

- Oxygen therapy, 2 L/min by nasal canula
- Furosemide (Lasix) 20-80 mg IV
- Nitroglycerine start at 10-20 mcg/min and titrate to BP (use with caution if inferior/right ventricular infarction suspected)
- Sublingual nitroglycerin 0.4 mg
- Morphine sulfate 2-4 mg IV. Avoid if inferior wall MI suspected or if hypotensive or presence of tenuous airway
- Potassium supplementation prn

**References:** See page 255.

# Hypertension

The age-adjusted prevalence of hypertension (systolic >140 and/or diastolic >90) in the United States is 32 percent in the black population and 23 percent in the white and Mexican-American populations. Hypertension is present in 65 and 80 percent of black men and women, respectively, over the age of 60. Comparable values in the white population are 55 and 65 percent. Hypertension is a major risk factor for coronary artery disease (CAD), heart failure, stroke, and renal failure.

## I.Definitions

**A.**The following definitions have been suggested by the seventh **Joint National Committee (JNC 7)**. Based upon the average of two or more readings at each of two or more visits after an initial screen, the following classification is used:
**1.**Normal blood pressure: systolic <120 mmHg and diastolic <80
**2.**Prehypertension: systolic 120-139 or diastolic 80-89
**3.**Hypertension:
Stage 1: systolic 140-159 or diastolic 90-99
Stage 2: systolic ≥160 or diastolic ≥100

**Classification and Management of Blood Pressure for Adults Aged 18 Years or Older**

| | | | | Initial drug therapy | |
|---|---|---|---|---|---|
| **BP classification** | **Systolic BP** | **Diastolic BP** | **Lifestyle Modification** | **Without compelling indication** | **With compelling indications** |
| Normal | <120 and | <30 | Encourage | | |
| Prehypertension | 120-139 or | 80-89 | Yes | No antihypertensive drug indicated | Drug(s) for the compelling indications |
| Stage 1 hypertension | 140-159 or | 90-99 | Yes | Thiazide-type diuretics for most, may consider ACE inhibitor, ARB, beta blocker, CCB, or combination | Drug(s) for the compelling indications Other antihypertensive drugs (diuretics, ACE inhibitor, ARB, beta blocker, CCB) as needed |
| Stage 2 hypertension | ≥160 or | ≥100 | Yes | 2-drug combination for most (usually thiazide-type diuretic and ACE inhibitor or ARB or beta blocker, CCB) | Drug(s) for the compelling indications Other antihypertensive drugs (diuretics, ACE inhibitor, ARB, beta blocker, CCB) as needed |

## II.Initial evaluation of the hypertensive patient

**A.**An evaluation should be performed to determine the extent of target organ damage and overall cardiovascular risk status. Identifiable (secondary) and curable causes of hypertension should be excluded.
**B.History**. The history should search for precipitating or aggravating factors, the extent of target organ damage,

and the presence of other risk factors for cardiovascular disease. The patient should also be asked about the signs and symptoms of identifiable causes of hypertension. The duration of hypertension should be determined.

**History in the Patient with Hypertension**

**Duration of hypertension**
- Last known normal blood pressure
- Course of the blood pressure

**Prior treatment of hypertension**
- Drugs: doses, side effects

**Intake of agents that may cause hypertension**
- Estrogens, sympathomimetics, adrenal steroids, excessive sodium

**Family history**
- Hypertension
- Premature cardiovascular disease or death
- Familial diseases: pheochromocytoma, renal disease, diabetes, gout

**Symptoms of secondary cause**
- Muscle weakness
- Spells of tachycardia, sweating, tremor
- Thinning of the skin
- Flank pain

**Symptoms of target organ damage**
- Headaches
- Transient weakness or blindness
- Loss of visual acuity
- Chest pain
- Dyspnea
- Claudication

**Other risk factors**
- Smoking
- Diabetes
- Dyslipidemias
- Physical inactivity

**Dietary history**
- Sodium
- Alcohol
- Saturated fats

**C.Physical examination.** The main goals on the physical examination are to evaluate for signs of end-organ damage (such as retinopathy) and for evidence of a cause of identifiable hypertension. The pulses should be palpated and the abdomen should be auscultated for a renal artery bruit. The presence of an upper abdominal bruit with a diastolic component that lateralizes toward one side is highly suggestive of renal artery stenosis.

**Physical Examination in the Patient with Hypertension**

Accurate measurement of blood pressure
General appearance: distribution of body fat, skin lesions, muscle strength, alertness
Funduscope
Neck: palpation and auscultation of carotids, thyroid Heart: size, rhythm, sounds Lungs: rhonchi, rales
Abdomen: renal masses, bruits over aorta or renal arteries, femoral pulses
Extremities: peripheral pulses, edema
Neurologic assessment

**D.Routine Laboratory testing**

**1.**Hematocrit, urinalysis, and routine blood chemistries (glucose, creatinine, electrolytes)

**2.**Lipid profile (total and HDL-cholesterol, triglycerides)

**3.12 lead electrocardiography** may document evidence of ischemic heart disease, rhythm and conduction disturbances, or left ventricular hypertrophy.

**E.Additional tests** may be indicated in certain settings:

**1.Limited echocardiography** is a more sensitive method to detect left ventricular hypertrophy than the ECG and is less expensive than a complete echocardiographic examination. The main indication for echocardiography is to detect possible end-organ damage in a patient with borderline blood pressure values.

**2.Ambulatory blood pressure monitoring** is indicated for persistent office hypertension but normal blood pressure readings in the ambulatory setting.

**3.Microalbuminuria testing** is indicated for patients with diabetes to screen for early nephropathy.

**4.Plasma renin activity** is performed in patients with possible low-renin forms of hypertension, such as primary hyperaldosteronism suggested by unexplained hypokalemia.

**5.Workup for renovascular hypertension** is indicated in patients in whom the history is suggestive. Spiral CT scanning or 3D time-of-flight MR angiography provide a minimally invasive and equally accurate alternative to angiography.

**Evaluation of Secondary Hypertension**

| | |
|---|---|
| **Renovascular Hypertension** | Captopril test: Plasma renin level before and 1 hr after captopril 25 mg. A greater than 150% increase in renin is positive<br>Captopril renography: Renal scan before and after 25 mg<br>MRI angiography<br>Arteriography (DSA) |
| **Hyperaldosteronism** | Serum potassium<br>Serum aldosterone and plasma renin activity<br>CT scan of adrenals |
| **Pheochromocytoma** | 24 hr urine catecholamines<br>CT scan<br>Nuclear MIBG scan |

| | |
|---|---|
| **Cushing's Syndrome** | Plasma cortisol<br>Dexamethasone suppression test |
| **Hyperparathyroidism** | Serum calcium<br>Serum parathyroid hormone |

**III. Treatment of hypertension**

**A.** All patients should undergo lifestyle (nonpharmacologic) modification.

**B.** In the absence of end-organ damage, a patient should not be labeled as having hypertension unless the blood pressure is persistently elevated after three visits over a several month period.

**Lifestyle Modifications in the Management of Hypertension**

| Modification | Recommendation | Systolic BP reduction |
|---|---|---|
| Weight reduction | Maintain normal body weight (BMI 18.5 to 24.9 kg/m$^2$) | 5-20 mmHg per 10-kg weight loss |
| Adopt eating plan | Consume a diet rich in fruits, vegetables, and low-fat dairy products with reduced saturated and total fat | 8 to 14 mmHg |
| Dietary sodium reduction | Reduce dietary sodium intake to no more than 2.4 g sodium or 6 gm sodium chloride | 2 to 8 mmHg |
| Physical activity | Engage in regular aerobic physical activity at least 30 minutes *per day,* most days of the week | 4 to 9 mmHg |
| moderation of alcohol consumption | Limit consumption to no more than 2 drinks per day in men and no more than 1 drink per day in women and lighter-weight persons | 2 to 4 mmHg |

The effects of modifications are not all additive.

**C.** Antihypertensive medications should be begun if the systolic pressure is persistently $\geq$140 mmHg and/or the diastolic pressure is persistently $\geq$90 mmHg despite nonpharmacologic therapy. Starting with two drugs may be considered in patients with a baseline blood pressure more than 20/10 mmHg above goal.

**D.** In patients with diabetes or chronic renal failure, antihypertensive therapy is indicated when the systolic pressure is persistently above 130 mmHg and/or the diastolic pressure is above 80 mmHg. A goal blood pressure below 130/85 mmHg is also recommended in patients with coronary heart disease.

**E. Prehypertension.** Patients with prehypertension (systolic 120-139 and/or diastolic 80-89), but without diabetes or chronic renal failure are treated with nonpharmacologic therapies such as weight reduction, sodium restriction, and avoidance of excess alcohol.

**F.** Individuals with prehypertension have an increased risk of cardiovascular events. Antihypertensive drug therapy should be considered among such patients if diabetes, end-organ damage and/or cardiovascular disease are present.

**IV. Initial therapy in essential hypertension**

**A. Initial therapy.** The seventh Joint National Committee (JNC 7) report recommends initiating therapy with a thiazide diuretic unless there is a specific indication for a drug from another class.

**1.** Low doses of a thiazide diuretic (eg, 12.5 to 25 mg of hydrochlorothiazide or chlorthalidone) are recommended. This regimen is associated with a low rate of metabolic complications, such as hypokalemia, glucose intolerance, and hyperuricemia.

**2.** If low-dose thiazide monotherapy fails to attain goal blood pressure in uncomplicated hypertensives, an ACE inhibitor/ARB, beta blocker, or calcium channel blocker can be sequentially added or substituted. An ACE inhibitor/ARB, which acts synergistically with a diuretic, is most often used.

| Considerations for individualizing Antihypertensive Therapy | |
|---|---|
| **Indication** | **Antihypertensive drugs** |
| **Compelling indications (major improvement in outcome independent of blood pressure)** | |
| Systolic heart failure | ACE inhibitor or ARB, beta blocker, diuretic, aldosterone antagonist |
| Post-myocardial infarction | ACE inhibitor, beta blocker, aldosterone antagonist |
| Proteinuric chronic renal failure | ACE inhibitor and/or ARB |
| High coronary disease risk | Diuretic, perhaps ACE inhibitor |
| Diabetes mellitus (no proteinuria) | Diuretic, perhaps ACE inhibitor |
| Angina pectoris | Beta blocker, calcium channel blocker |
| Atrial fibrillation rate control | Beta blocker, nondihydropyridine calcium channel blocker |
| Atrial flutter rate control | Beta blocker, nondihydropyridine calcium channel blocker |
| **Likely to have a favorable effect on symptoms in comorbid conditions** | |
| Essential tremor | Beta blocker (noncardioselective) |
| Hyperthyroidism | Beta blocker |
| Migraine | Beta blocker, calcium channel blocker |
| Osteoporosis | Thiazide diuretic |
| Raynaud's syndrome | Dihydropyridine calcium channel blocker |

| Contraindications to Specific Antihypertensive Agents | |
|---|---|
| **Indication** | **Antihypertensive drugs** |
| Angioedema | ACE inhibitor |
| Bronchospastic disease | Beta blocker |
| Pregnancy | ACE inhibitor, ARB (includes women likely to become pregnant) |
| Second or third degree heart block | Beta blocker, nondihydropyridine calcium channel blocker |
| **May have adverse effect on comorbid conditions** | |
| Depression | Beta blocker, central alpha agonist |
| Gout | Diuretic |
| Hyperkalemia | Aldosterone antagonist, ACE inhibitor, ARB |
| Hyponatremia | Thiazide diuretic |
| Renovascular disease | ACE inhibitor or ARB |

**B.Indications for specific drugs.** Recommendations for initial therapy should be amended in certain clinical settings in which specific agents might offer particular benefit.

**1.Diuretics**. A low dose thiazide diuretic in both younger and older patients provides better cardioprotection than an ACE inhibitor or a calcium channel blocker in patients with risk factors for coronary artery disease, including left ventricular hypertrophy, type 2 diabetes, previous myocardial infarction or stroke, current cigarette smoking habits, hyperlipidemia, or atherosclerotic cardiovascular disease.

| Thiazide Diuretics | |
|---|---|
| **Drug** | **Usual dose** |
| Hydrochlorothiazide (HCTZ, Hydrodiuril) | 12.5-25 mg qd |
| Chlorthalidone (Hygroton) | 12.5-25 mg qd |
| Chlorothiazide (Diuril) | 125-500 mg qd |
| Indapamide (Lozol) | 1.25 mg qd |
| Metolazone (Zaroxolyn) | 1.25-5 mg qd |

**2.ACE inhibitors.** ACE inhibitors provide survival benefits in patients with heart failure and myocardial infarction (particularly ST elevation) and renal benefits in patients with proteinuric chronic renal failure. Thus, an ACE inhibitor should be used in patients with heart failure, prior myocardial infarction, asymptomatic left ventricular dysfunction, type 1 diabetics with nephropathy, and nondiabetic proteinuric chronic renal failure.

| Angiotensin-converting enzyme inhibitors | | |
|---|---|---|
| **Drug** | **Usual doses** | **Maximum dose** |
| Benazepril (Lotensin) | 10-40 mg qd or divided bid | 80 mg/d |
| Captopril (Capoten) | 50 mg bid-qid | 450 mg/d |
| Enalapril (Vasotec, Vasotec IV) | 10-40 mg qd or divided bid | 40 mg/d |
| Fosinopril (Monopril) | 20-40 mg qd or divided bid | 80 mg/d |
| Lisinopril (Prinivil, Zestril) | 20-40 mg qd | 40 mg/d |
| Moexipril (Univasc) | 15-30 mg qd | 30 mg/d |
| Quinapril (Accupril) | 20-80 mg qd or divided bid | 80 mg/d |
| Ramipril (AItace) | 5-20 mg qd or divided bid | 20 mg/d |
| Trandolapril (Mavik) | 1-4 mg qd | 8 mg/d |
| Perindopril (Aceon) | 4-8 mg qd-bid | 8 mg/d |

**3.**ACE inhibitors or angiotensin II receptor blockers should be part of the therapeutic regimen in all patients with coronary disease.
**4.Angiotensin-II Receptor Blockers (ARBs)**. The indications for and efficacy of ARBs are not different from those with ACE inhibitors. An ARB is indicated in patients who do not tolerate ACE inhibitors (because of cough).

| Angiotensin II Receptor Blockers | | |
|---|---|---|
| **Drug** | **Usual dose** | **Maximum dose** |
| Losartan (Cozaar) | 50 mg qd | 100 mg/d |
| Candesartan (Atacand) | 4-8 mg qd | 16 mg/d |
| Eprosartan (Teveten) | 400-800 mg qd | 800 mg/d |
| Irbesartan (Avapro) | 150-300 mg qd | 300 mg/d |
| Telmisartan (Micardis) | 40-80 mg qd | 80 mg/d |
| Valsartan (Diovan) | 80 mg qd | 320 mg/d |

**5.Beta blockers.** A beta blocker without intrinsic sympathomimetic activity should be given after an acute myocardial infarction and to stable patients with heart failure or asymptomatic left ventricular dysfunction (beginning with very low doses). The use of beta blockers in these settings is in addition to the recommendations for ACE inhibitors in these disorders. Beta blockers are also given for rate control in atrial fibrillation, for control of angina, and for symptom control in a number of other disorders.

| Beta-blockers | | |
|---|---|---|
| **Drug** | **Usual dose** | **Maximum dose** |
| Acebutolol (Sectral) | 200-800 mg/d (qd or bid) | 1.2 g/d (bid) |
| Atenolol (Tenormin) | 50-100 mg qd | 100 mg qd |
| Betaxolol (Kerlone) | 10 mg qd | 20 mg qd |
| Bisoprolol (Zebeta) | 5 mg qd | 20 mg qd |
| Carteolol (Cartrol) | 2.5 mg qd | 10 mg qd |
| Carvedilol (Coreg) | 6.26-25 mg bid | 100 mg/d |
| Labetalol (Normodyne, Trandate) | 100-600 mg bid | 1200 mg/d |
| Metoprolol (Toprol XL) | 100-200 mg qd | 400 mg qd |
| Metoprolol (Lopressor) | 100-200 mg/d (qd or bid) | 450 mg/d (qd or bid) |
| Nadolol (Corgard) | 40 mg qd | 320 mg/d |
| Penbutolol(Levatol ) | 20 mg qd | NA |
| Pindolol (Visken) | 5 mg bid | 60 mg/d |
| Propranolol (Inderal, Inderal LA) | 120-160 mg qd (LA 640 mg/d) | |
| Timolol (Blocadren) | 10-20 mg bid | 60 mg/d (bid) |

**6.Calcium channel blockers**. There are no absolute indications for calcium channel blockers in hypertensive patients. Like beta blockers, they can be given for rate control in patients with atrial fibrillation or for control of angina. Calcium channel blockers may be preferred in patients with obstructive airways disease.

| Calcium channel blockers | |
|---|---|
| **Drug** | **Dosage** |
| Diltiazem extended-release (Cardizem SR) | 120-360 mg in 2 doses |
| Diltiazem CD (Cardizem CD) | 120-360 mg in 1 dose |
| Diltiazem XR (Dilacor XR) | 120-480 mg in 1 dose |
| Verapamil (Calan) | 120-480 mg in 2 or 3 doses |
| Verapamil extended-release (Calan SR) | 120-480 mg in 1 or 2 doses |
| Verapamil HS (Covera-HS) | 180-480 mg in 1 dose |
| **Dihydropyridines** | |
| Amlodipine (Norvasc) | 2.5-10 mg in 1 dose |
| Felodipine (Plendil) | 2.5-10 mg in 1 dose |
| Isradipine (DynaCirc) | 5-10 mg in 2 doses |
| Isradipine extended-release (DynaCirc CR) | 5-10 mg in 1 dose |
| Nicardipine (Cardene) | 60-120 mg in 3 doses |
| Nicardipine extended-release (Cardene SR) | 60-120 mg in 2 doses |
| Nifedipine extended-release (Adalat CC, Procardia XL) | 30-90 mg in 1 dose |
| Nisoldipine (Sular) | 10-60 mg in 1 dose |

**C.Combination therapy**

**1.**Administering two drugs as initial therapy should also be considered in patients with blood pressures that are more than 20/10 mmHg above goal blood pressures.

**2.**If two drugs are required, use of a low dose of a thiazide diuretic as one of the drugs increases the response rate to all other agents. By minimizing volume expansion, diuretics tend to increase the antihypertensive effect of all other antihypertensive drugs.

**3.**The combination of a thiazide diuretic with a beta blocker or an ACE inhibitor has a synergistic effect, controlling the BP in up to 85 percent of patients. The beta blocker or the ACE inhibitor minimizes diuretic-induced metabolic abnormalities (such as hypokalemia, hyperuricemia and hyperlipidemia).

**D.Fixed dose combinations**. A wide variety of (low) dose combination preparations are available, including

low doses of a diuretic with a beta blocker, ACE inhibitor, or ARB:

**1.**Tarka: Sustained release verapamil (180 mg) - trandolapril (2 mg)

**2.**Tenoretic: Atenolol (100 mg) - chlorthalidone (25 mg)

**3.**Zestoretic: Lisinopril (20 mg) - hydrochlorothiazide (12.5 mg)

**4.**The three combinations are equally effective, normalizing the blood pressure or lowering the diastolic pressure by more than 10 mmHg in 69 to 76 percent of patients. All are well tolerated.

**Combination Agents for Hypertension**

| Drug | Initial dose | Comments |
|---|---|---|
| **Beta-Blocker/Diuretic** | | |
| Atenolol/chlorthalidone (Tenoretic) | 50 mg/25 mg, 1 tab qd | Additive vasodilation |
| Bisoprolol/HCTZ (Ziac) | 2.5 mg/6.25 mg, 1 tab qd | |
| Metoprolol/HCTZ (Lopressor HCTZ) | 100 mg/25 mg, 1 tab qd | |
| Nadolol/HCTZ (Corzide) | 40 mg/5 mg, 1 tab qd | |
| Propranolol/HCTZ (Inderide LA) | 80 mg/50 mg, 1 tab qd | |
| Timolol/HCTZ (Timolide) | 10 mg/25 mg, 1 tab qd | |
| **ACE inhibitor/Diuretic** | | |
| Benazepril/HCTZ (Lotensin HCT) | 5 mg/6.25 mg, 1 tab qd | ACE inhibitor conserves potassium and magnesium; combination beneficial for CHF patients with HTN |
| Captopril/HCTZ (Capozide) | 25 mg/15 mg, 1 tab qd | |
| Enalapril/HCTZ (Vaseretic) | 5 mg/12.5 mg, 1 tab qd | |
| Lisinopril/HCTZ (Zestoretic, Prinzide) | 10 mg/12.5 mg, 1 tab qd | |
| Moexipril/HCTZ (Uniretic) | 7.5 mg/12.5 mg, 1 tab qd | |
| **ACE inhibitor/Calcium-channel blocker** | | |
| Benazepril/amlodipine (Lotrel) | 2.5 mg/10 mg, 1 tab qd | |
| Enalapril/felodipine (Lexxel) | 5 mg/5 mg, 1 tab qd | |
| Enalapril/diltiazem (Teczem) | 5 mg/180 mg, 1 tab qd | |
| Trandolapril/verapamil (Tarka) | 2 mg/180 mg, 1 tab qd | |
| **Angiotensin II receptor blocker/Diuretic** | | |
| Losartan/HCTZ (Hyzaar) | 50 mg/12.5 mg, 1 tab qd | |
| Valsartan/HCTZ (Diovan HCT) | 80 mg/12.5 mg, 1 tab qd | |
| **Alpha-1-Blocker/Diuretic** | | |
| Prazosin/polythiazide (Minizide) | 1 mg/0.5 mg, 1 cap bid | Synergistic vasodilation |
| **$K^+$-sparing diuretic/Thiazide** | | |
| Amiloride/HCTZ (Moduretic) | 5 mg/50 mg, 1 tab qd | Electrolyte-sparing effect |
| Triamterene/HCTZ (Dyazide, Maxzide) | 37.5 mg/25 mg, 1/2 tab qd | |

**References:** See page 255.

## Atrial Fibrillation

Atrial fibrillation (AF) is the most common cardiac rhythm disturbance. Hemodynamic impairment and thromboembolic events result in significant morbidity and mortality.

**I.Pathophysiology**

**A.Atrial fibrillation (AF)** is characterized by impaired atrial mechanical function. The ECG is characterized by the replacement of consistent P waves by rapid oscillations or fibrillatory waves that vary in size, shape, and timing, associated with an irregular ventricular response.

**B.**The prevalence of AF is 0.4%, increasing with age. It occurs in more than 6% of those over 80 years of age. The rate of ischemic stroke among patients with nonrheumatic AF averages 5% per year.

**II.Causes and associated conditions**

**A.Acute causes of AF.** AF can be related to excessive alcohol intake, surgery, electrocution, myocarditis, pulmonary embolism, and hyperthyroidism.

**B.AF without associated cardiovascular disease.** In younger patients, 20% to 25% of cases of AF occur as lone AF.

**C.AF with associated cardiovascular disease.** Cardiovascular conditions associated with AF include valvular heart disease (most often mitral), coronary artery disease (CAD), and hypertension.

**III.Clinical manifestations**

**A.**AF can be symptomatic or asymptomatic. Patients with AF may complain of palpitations, chest pain, dyspnea, fatigue, lightheadedness, or polyuria. Syncope is uncommon.

**B.Evaluation of the patient with atrial fibrillation**

**1.**The initial evaluation of a patient with suspected or proven AF includes characterizing the pattern of the arrhythmia as paroxysmal or persistent, determining its cause, and defining associated cardiac and factors.

**2.**The physical examination may reveal an irregular pulse, irregular jugular venous pulsations, and variation in the loudness of the first heart sound. Examination may disclose valvular heart disease, myocardial abnormalities, or heart failure.

**3.Investigations.** The diagnosis of AF requires ECG documentation. If episodes are intermittant, then a 24-h Holter monitor can be used. Additional investigation may include transesophageal echocardiography.

**IV.Management of atrial fibrillation**

**A.**In patients with persistent AF, the dysrhythmia may be managed by restoration of sinus rhythm, or AF may be allowed to continue while the ventricular rate is controlled.

**B.Cardioversion**

**1.**Cardioversion is often performed electively to restore sinus rhythm. The need for cardioversion can be immediate when the arrhythmia causes acute HF, hypotension, or angina pectoris. Cardioversion carries a risk of thromboembolism unless anticoagulation prophylaxis is initiated before the procedure; this risk is greatest when the arrhythmia has been present more than 48 hours.

**2.Methods of cardioversion.** Cardioversion can be achieved by drugs or electrical shocks. The development of new drugs has increased the popularity of pharmacological cardioversion. **Pharmacological cardioversion** is most effective when initiated within seven days after the onset of AF. **Direct-current cardioversion** involves a synchronized electrical shock. Cardioversion is performed with the patient having fasted and under anesthesia. An initial energy of 200 J or greater is recommended.

**C.Maintenance of sinus rhythm**

**1.**Maintenance of sinus rhythm is relevant in patients with paroxysmal AF and persistent AF (in whom cardioversion is necessary to restore sinus rhythm).

**2.Approach to antiarrhythmic drug therapy**

**a.**Prophylactic drug treatment is seldom indicated after the first-detected episode of AF and can be avoided in patients with infrequent and well-tolerated paroxysmal AF.

**b.**Beta-blockers can be effective in patients who develop AF only during exercise.

**c.In patients with lone AF,** a beta-blocker may be tried first, but flecainide, propafenone, and sotalol are particularly effective. Amiodarone and dofetilide are recommended as alternative therapy. Quinidine, procainamide, and disopyramide are not favored unless amiodarone fails or is contraindicated.

**d.**The anticholinergic activity of long-acting disopyramide makes it a relatively attractive choice for patients with vagally induced AF.

**Drugs Used to Maintain Sinus Rhythm in Atrial Fibrillation**

| Drug | Daily Dosage | Potential Adverse Effects |
|---|---|---|
| Amiodarone | 100–400 mg | Photosensitivity, pulmonary toxicity, polyneuropathy, GI upset, bradycardia, torsade de pointes (rare), hepatic toxicity, thyroid dysfunction |
| Disopyramide | 400–750 mg | Torsade de pointes, HF, glaucoma, urinary retention, dry mouth |
| Dofetilide | 500–1000 mcg | Torsade de pointes |
| Flecainide | 200–300 mg | Ventricular tachycardia, congestive HF, conversion to atrial flutter |
| Procainamide | 1000–4000 mg | Torsade de pointes, lupus-like syndrome, GI symptoms |
| Propafenone | 450–900 mg | Ventricular tachycardia, congestive HF, conversion to atrial flutter |
| Quinidine | 600–1500 mg | Torsade de pointes, GI upset, conversion to atrial flutter |
| Sotalol | 240–320 mg | Torsade de pointes, congestive HF, bradycardia, exacerbation of chronic obstructive or bronchospastic lung disease |

**3.Nonpharmacological correction of atrial fibrillation**

**a.A surgical procedure** (maze operation) controls AF in more than 90% of selected patients.

**b.Catheter ablation** eliminates or reduces the frequency of recurrent AF in more than 60% of patients, but the risk of recurrent AF is 30% to 50%. This procedure has not been widely applied.

**D.Rate control during atrial fibrillation**

**1.Pharmacological approach.** An alternative to maintenance of sinus rhythm in patients with paroxysmal or persistent AF is control of the ventricular rate. The rate is controlled when the ventricular response is between 60 and 80 bpm at rest and between 90 to 115 bpm during moderate exercise.

**a.**Anticoagulation is recommended for 3 to 4 weeks before and after cardioversion for patients with AF of unknown duration or that has lasted more than 48 h. When acute AF produces hemodynamic instability, immediate cardioversion should not be delayed, but intravenous heparin or low-molecular-weight heparin should be administered first.

**Intravenous Agents for Heart Rate Control in Atrial Fibrillation**

| Drug | Loading Dose | Onset | Maintenance Dose | Major Side Effects |
|---|---|---|---|---|
| Diltiazem | 0.25 mg/kg IV over 2 min | 2–7 min | 5–15 mg per hour infusion | Hypotension, heart block, HF |
| Esmolol | 0.5 mg/kg over | 1 min | 0.05–0.2 mg/kg/min | Hypotension, heart block, bradycardia, asthma, HF |
| Metoprolol | 2.5–5 mg IV bolus over 2 min up to 3 doses | 5 min | NA | Hypotension, heart block, bradycardia, asthma, HF |
| Propranolol | 0.15 mg/kg IV | 5 min | | Hypotension, heart block, bradycardia, asthma, HF |
| Verapamil | 0.075–0.15 mg/kg IV over 2 min | 3–5 min | | Hypotension, heart block, HF |
| Digoxin | 0.25 mg IV each 2 h, up to 1.5 mg | 2 h | 0.125–0.25 mg daily | Digitalis toxicity, heart block, bradycardia |

**Oral Agents for Heart Rate Control**

| Drug | Loading Dose | Usual Maintenance Dose | Major Side Effects |
|---|---|---|---|
| Digoxin | 0.25 mg PO each 2 h ; up to 1.5 mg | 0.125–0.375 mg daily | Digitalis toxicity, heart block, bradycardia |
| Diltiazem | NA | 120–360 mg daily in divided doses; slow release available | Hypotension, heart block, HF |
| Metoprolol | NA | 25–100 mg BID | Hypotension, heart block, bradycardia, asthma, HF |
| Propranolol | NA | 80–240 mg daily in divided doses | Hypotension, heart block, bradycardia, asthma, HF |
| Verapamil | NA | 120–360 mg daily in divided doses; slow release available | Hypotension, heart block, HF, digoxin interaction |
| Amiodarone | 800 mg daily for 1 wk<br>600 mg daily for 1 wk<br>400 mg daily for 4–6 wk | 200 mg daily | Pulmonary toxicity, skin discoloration, hypothyroidism, corneal deposits, optic neuropathy, warfarin interaction, proarrhythmia |

**V.Prevention of thromboembolic complications**

**A.**Atrial fibrillation is the underlying cause of 30,000 to 40,000 embolic strokes per year. The incidence of these strokes increases with age, rising from 1.5 percent in patients aged 50 to 59 years to 23.5 percent in patients aged 80 to 89 years.

**B.**Risk factors for stroke in patients with atrial fibrillation include a history of transient ischemic attack or ischemic stroke, age greater than 65 years, a history of hypertension, the presence of a prosthetic heart valve, rheumatic heart disease, left ventricular systolic dysfunction, or diabetes.

## VI.Anticoagulant drugs

### A.Heparin

**1.**Heparin is the preferred agent for initial anticoagulation. The drug should be given as an intravenous infusion, with the dose titrated to achieve an activated partial thromboplastin time of 1.5 to 2.5. Heparin 80 U/kg load, 18 U/kg/hr drip.

**2.**Heparin should not be used in patients with signs of active bleeding. Its use in patients with acute embolic stroke should be guided by the results of transesophageal echocardiography to detect atrial thrombi.

**3.**In patients with atrial fibrillation that has persisted for more than 48 hours, heparin can be used to reduce the risk of thrombus formation and embolization until the warfarin level is therapeutic or cardioversion is performed.

**B.Warfarin (Coumadin).** Chronic warfarin therapy is commonly used to prevent thromboembolic complications in patients with atrial fibrillation. Warfarin therapy is monitored using the International Normalized Ratio (INR), which is derived from the prothrombin time. Risk factors for major bleeding include poorly controlled hypertension, propensity for falling, dietary factors, interactions with concomitant medications, and patient noncompliance. The INR should be kept between 2.0 and 3.0.

**C.Aspirin.** If bleeding risk prohibits the use of warfarin, aspirin is an alternative. Aspirin inhibits platelet aggregation and thrombus formation. Aspirin is slightly less effective than warfarin in preventing stroke in patients with atrial fibrillation, but it is safer in patients at high risk for bleeding.

## VII.Anticoagulation during cardioversion

### A.Early cardioversion

**1.**Early medical or electrical cardioversion may be instituted without prior anticoagulation therapy when atrial fibrillation has been present for less than 48 hours. However, heparin is routinely used.

**2.**If the duration of atrial fibrillation exceeds 48 hours or is unknown, transesophageal echocardiography (to rule out atrial thrombi) followed by early cardioversion is recommended. Heparin therapy should be instituted during transesophageal echocardiography. If no atrial thrombi are observed, cardioversion can be performed. If atrial thrombi are detected, cardioversion should be delayed and anticoagulation continued. To decrease the risk of thrombus extension, heparin should be continued, and warfarin therapy should be initiated. Once the INR is above 2.0, heparin can be discontinued, but warfarin should be continued for four weeks.

**3.**If cardioversion is unsuccessful and patients remain in atrial fibrillation, warfarin or aspirin may be considered for long-term prevention of stroke.

### B.Elective cardioversion

**1.Warfarin (Coumadin)** should be given for three weeks before elective electrical cardioversion is performed. The initial dose is 5 to 10 mg per day. After successful cardioversion, warfarin should be continued for four weeks to decrease the risk of new thrombus formation.

**2.**If atrial fibrillation recurs or patients are at high risk for recurrent atrial fibrillation, warfarin may be continued indefinitely, or aspirin therapy may be considered. Factors that increase the risk of recurrent atrial fibrillation include an enlarged left atrium and left ventricular dysfunction.

**Antithrombotic Therapy in Cardioversion for Atrial Fibrillation**

| Timing of cardioversion | Anticoagulation |
|---|---|
| Early cardioversion in patients with atrial fibrillation for less than 48 hours | Heparin during cardioversion period to achieve PTT of 1.5 to 2.5. Heparin 80 U/kg load, 18 U/kg/hr drip. |
| Early cardioversion in patients with atrial fibrillation for more than 48 hours or an unknown duration, but without documented atrial thrombi | Heparin during cardioversion period to achieve PTT of 1.5 to 2.5<br>Warfarin (Coumadin) for 4 weeks after cardioversion to achieve target INR of 2.5 (range: 2.0 to 3.0) |
| Elective cardioversion in patients with atrial fibrillation for more than 48 hours or an unknown duration | Warfarin for 3 weeks before and 4 weeks after cardioversion to achieve target INR of 2.5 (range: 2.0 to 3.0) |

## VIII.Long-term anticoagulation

**A.**Long-term anticoagulation therapy should be considered in patients with persistent atrial fibrillation who have failed cardioversion and in patients who are not candidates for medical or electrical cardioversion. Patients with a significant risk of falling, a history of noncompliance, active bleeding, or poorly controlled hypertension should not receive long-term anticoagulation therapy.

**B.** Factors that significantly increase the risk for stroke include previous stroke, previous transient cerebral ischemia or systemic embolus, hypertension, poor left ventricular systolic function, age greater than 75 years, prosthetic heart valve, and history of rheumatic mitral valve disease. With persistent atrial fibrillation, patients older than 65 years and those with diabetes are also at increased risk. The lowest risk for stroke is in patients with atrial fibrillation who are less than 65 years of age and have no history of cardiovascular disease, diabetes, or hypertension.

**C.** Warfarin therapy has been shown to reduce the absolute risk of stroke by 0.8 percent per year, compared with aspirin. In patients with a history of stroke, warfarin reduces the absolute risk of stroke by 7 percent per year.

**Recommendations for Anticoagulation in Atrial Fibrillation**

Heparin therapy should be considered in hospitalized patients with atrial fibrillation persisting beyond 48 hours and in patients undergoing medical (pharmacologic) or electrical cardioversion. Heparin 80 U/kg load, 18 U/kg/hr drip.

Antithrombotic therapy using warfarin (Coumadin) should be given for 3 weeks before cardioversion and 4 weeks after successful cardioversion. The initial dose is 5 to 10 mg per day, with the daily dose then adjusted according to the INR.

Patients with persistent or recurrent atrial fibrillation after attempted cardioversion should be given chronic warfarin or aspirin therapy for stroke prevention.

Warfarin is the preferred agent in patients at high risk for stroke because of previous stroke, age over 75 years, and/or poor left ventricular function.

Aspirin is the preferred agent in patients at low risk for stroke and in patients with a risk of falling, history of noncompliance, active bleeding, and/or poorly controlled hypertension.

**References:** See page 255.

## Hypercholesterolemia

The Third Report of the Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III or ATP III) summarizes the current management of high serum cholesterol.

**I. Identification of patients at risk**

**A.** The ATP III recommendations that treatment of hypercholesterolemia be based upon the LDL-cholesterol fraction and influenced by the coexistence of CHD and the number of cardiac risk factors.

**Step 1.** The first step in determining patient risk is to obtain a fasting lipid profile.

**Classification of LDL, Total, and HDL Cholesterol (mg/dL)**

| | |
|---|---|
| **LDL Cholesterol** | |
| <100 | Optimal |
| 100-129 | Near optimal/above optimal |
| 130-159 | Borderline high |
| 160-189 | High |
| ≥190 | Very high |
| **Total Cholesterol** | |
| <200 | Desirable |
| 200-239 | Borderline high |
| ≥240 | High |
| **HDL Cholesterol** | |
| <40 | Low |
| ≥60 | High |

**Step 2.** CHD equivalents, risk factors that place the patient at similar risk for CHD events as a history of CHD itself, should be identified in step 2:

1. Diabetes mellitus
2. Symptomatic carotid artery disease
3. Peripheral arterial disease
4. Abdominal aortic aneurysm

**Step 3.** Major CHD factors other than LDL are identified in step 3:

1. Cigarette smoking
2. Hypertension (BP 140/90 or antihypertensive medication)
3. Low HDL cholesterol (<40 mg/dL)
4. Family history of premature CHD (in male first degree relatives <55 years, in female first degree relatives <65 years)
5. Age (men 45 years, women 55 years)

6. HDL cholesterol 60 mg/dL counts as a "negative" risk factor; its presence removes one risk factor from the total count.

**Step 4.** If two or more risk factors other than LDL (as defined in step 3) are present in a patient without CHD or a CHD equivalent (as defined in step 2), the 10-year risk of CHD is assessed using Framingham risk tables.

**Step 5.** The last step in risk assessment is to determine the risk category that establishes the LDL goal, when to initiate therapeutic lifestyle changes, and when to consider drug therapy.

**LDL Cholesterol Goals for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories.**

| Risk Category | LDL-C Goal | LDL Level at Which to Initiate Therapeutic Lifestyle Changes | LDL Level at Which to Consider Drug Therapy |
|---|---|---|---|
| CHD | <100 mg/dL | ≥100 mg/dL | ≥130 mg/dL (100-129 mg/dL: drug optional) |
| 2+ Risk Factors | <130 mg/dL | ≥130 mg/dL | 10-year risk 10-20%:≥130 mg/dL |
| | | | 10-year risk <10%:≥160 mg/dL |
| 0-1 Risk Factor | <160 mg/dL | ≥160 mg/dL | ≥190 mg/dL (160-189 mg/dL: LDL-lowering drug optional) |

**II.Treatment**

**A.**Cardiovascular benefits of cholesterol lowering with statin drugs have been demonstrated in the following groups:

**1.**Patients with CHD, with or without hyperlipidemia

**2.**Men with hyperlipidemia but no known CHD

**3.**Men and women with average total and LDL cholesterol levels and no known CHD

**B.Secondary prevention.** In patients who already have CHD, a goal LDL-cholesterol value of less than 100 mg/dL is recommended for secondary prevention. Dietary modification should be employed in any patient with CHD and an LDL-cholesterol exceeding 100 mg/dL, and drug therapy should be considered if the LDL-cholesterol remains above 130 mg/dL.

**C.Primary prevention. The serum LDL-cholesterol concentration and risk factor status determine the suggested approach:**

**1.**Individuals with desirable serum LDL-cholesterol values may be reevaluated in five years, while those with borderline high-risk values and less than two cardiac risk factors should be reevaluated in one year (one risk factor is subtracted if the serum HDL is 60 mg/dL).

**2.**A cholesterol lowering diet is indicated in patients with a high-risk serum LDL-cholesterol concentration and in those with borderline high-risk values plus two or more cardiac risk factors.

**3.**Drug therapy with a statin should be considered if, after a trial of dietary modification, serum LDL-cholesterol remains above 190 mg/dL in any patient or above 160 mg/dL in a patient with two or more CHD risk factors.

**4.**The goal serum LDL-cholesterol concentration should be below 160 mg/dL in patients with less than two CHD risk factors. A lower value of 130 mg/dL is recommended in patients with two or more CHD risk factors.

**D.Patients with low HDL.** Therapy aimed at raising HDL levels into the normal range has been advocated in patients with overt CHD and those at high risk because of a strong family history. Low HDL cholesterol is defined as <40 mg/dL.

**E.Hypertriglyceridemia** should be treated in patients who also have hypercholesterolemia. Possible indications for treatment of isolated hypertriglyceridemia include overt CHD, a strong family history of CHD, multiple coexisting cardiac risk factors, and very high triglyceride levels (>1000 mg/dL).

**F.Lifestyle modifications** include reductions in dietary fat, weight loss in overweight patients, and aerobic exercise. All patients with high LDL cholesterol should undergo lifestyle modifications. Many will not reach the goal level of cholesterol and will require drug therapy.

**G.Drug therapy**

**1.Statins** are commonly used in the treatment of hypercholesterolemia. They are the most powerful drugs for lowering LDL cholesterol, with reductions of 20 to 60%. Fluvastatin (Lescol) is somewhat less potent, decreasing LDL by 20-25%. Atorvastatin is the most potent, reducing LDL by 29-61%. An additional benefit of atorvastatin is more effective triglyceride lowering (14 to 33%). Adverse reactions occur less frequently with the statins than with other lipid-lowering agents.

**2.Cholesterol absorption inhibitors - Ezetimibe (Zetia)** modestly lowers the LDL cholesterol when used alone, but may have its greatest use in combination with statins. It does not have the gastrointestinal effects of the bile acid sequestrants. It is more effective in

lowering LDL cholesterol than doubling the dose of the statin.

**Dose, Side Effects, and Drug Interactions of Lipid-Lowering Drugs**

| Drug class | Dose | Dosing | Major side effects and drug interactions |
|---|---|---|---|
| **HMG CoA reductase inhibitors** | | | |
| Atorvastatin (Lipitor)<br>Lovastatin (generic, Mevacor)<br>Extended-release lovastatin (Altocor)<br>Pravastatin (Pravachol)<br>Simvastatin (Zocor)<br>Fluvastatin (Lescol, Lescol XL)<br>Rosuvastatin (Crestor) | 10-40 mg/day<br>20-80 mg/day<br><br>10-60 mg/day<br><br>10-40 mg/day<br><br>5-40 mg/day<br>10-40 mg/day<br><br>10-40 mg/day | Take at bedtime. Take BID if dose >20 mg/day. | Headache; nausea; sleep disturbance; elevations in liver enzymes and alkaline phosphatase. Myositis and rhabdomyolysis. Lovastatin and simvastatin potentiate warfarin and increase digoxin levels |
| **Cholesterol absorption inhibitors** | | | |
| Ezetimibe (Zetia) | 10 mg/day | 10 mg qd | Increased transaminases in combination with statins |
| **Bile acid sequestrants** | | | |
| Cholestyramine (Questran, Questran Lite)<br>Colestipol (Colestid)<br>Colesevelam (Welchol) | 4-24 g/day<br><br>5-30 g/day<br>3.75 gm once or divided BID | Take within 30 min of meal. A double dose with dinner produces same effect as BID dosing | Nausea, bloating, cramping, constipation; elevations in hepatic transaminases and alkaline phosphatase. Impaired absorption of fat soluble vitamins, digoxin, warfarin, thiazides, beta-blockers, thyroxine, phenobarbital. |
| **Nicotinic acid** | 1-12 g/day | Given with meals. Start with 100 mg BID and titrate to 500 mg TID. After 6 weeks, check lipids, glucose, liver function, and uric acid. | Prostaglandin-mediated cutaneous flushing, headache, pruritus; hyperpigmentation; acanthosis nigricans; dry skin; nausea; diarrhea; myositis. |
| **Fibrates** | | | |
| Gemfibrozil (Lopid) | 600 mg BID | 50 to 60 min before meals. | Potentiates warfarin. Absorption of gemfibrozil diminished by bile acid sequestrants. |
| Fenofibrate (Lofibra, micronized) | 200 mg qd | Take with breakfast. Use lower dosage with renal insufficiency. | Skin rash, nausea, bloating, cramping, myalgia; lowers cyclosporin levels; nephrotoxic in cyclosporin-treated patients. |
| Fenofibrate (Tricor) | 160 mg qd | | |
| **Probucol** | 500 mg BID | | Loose stools; eosinophilia; QT prolongation; angioneurotic edema. |
| **Extended-release niacin plus (immediate-release) lovastatin (Advicor)** | 1000 mg/40 mg/day | 1000 mg + 40 mg h.s.3 | markedly lowers LDL and triglycerides and raises HDL |

| Average Reduction in LDL Levels with Statin Drugs | | | | |
|---|---|---|---|---|
| **Statin** | **10-mg dosage** | **20-mg dosage** | **40-mg dosage** | **80-mg dosage** |
| Atorvastatin (Lipitor) | 38% | 46% | 51% | 54% |
| Simvastatin (Zocor) | 28% | 35% | 40% | 48% |
| Lovastatin (Mevacor, generic) | -- | 29% | 31% | 48% |
| Cerivastatin (Baycol) | 0.2-mg dosage: 25% | 0.3-mg dosage: 30% | 0.4-mg dosage: 36% | 0.8-mg dosage: 44% |
| Pravastatin (Pravachol) | 19% | 24% | 34% | 40% |
| Fluvastatin (Lescol) | -- | 17% | 23% | 33% |

**3.Fibrates** (gemfibrozil, clofibrate, fenofibrate) primarily lower plasma triglyceride and raise HDL levels. They are effective for the treatment of hypertriglyceridemia and combined hyperlipidemia.

**4.Bile acid sequestrants** are effective in patients with mild to moderate elevations of LDL cholesterol. Bile acid sequestrants are also effective when used with a statin or nicotinic acid. Use is often limited by side effects.

**5.Nicotinic acid** is effective in patients with hypercholesterolemia and in combined hyperlipidemia associated with normal and low levels of HDL cholesterol. Use is often limited by poor tolerability.

**6.Probucol** modestly lowers LDL cholesterol, but more prominently reduces HDL cholesterol. Probucol should be limited to refractory hypercholesterolemia or familial hypercholesterolemia and xanthomas.

**References:** See page 255.

# Pulmonary Disorders

## Allergic Rhinitis

Allergic rhinitis is characterized by paroxysms of sneezing, rhinorrhea, nasal obstruction, and itching of the eyes, nose, and palate. It is also frequently associated with postnasal drip, cough, irritability, and fatigue. Allergic rhinitis is classified as seasonal if symptoms occur at a particular time of the year, or perennial if symptoms occur year round.

**I.Pathophysiology**

**A.**Common allergens causing seasonal allergic rhinitis are tree, grass, and weed pollens, and fungi. Dust mites, cockroaches, animal proteins, and fungi are frequently associated with perennial rhinitis.

**B.**Perennial allergic rhinitis is associated with nasal symptoms, which occur for more than nine months of the year. Perennial allergic rhinitis usually reflects allergy to indoor allergens like dust mites, cockroaches, or animal dander.

**C.**Nine to 40 percent of the population may have some form of allergic rhinitis. The prevalence of allergic rhinitis has a bimodal peak in the early school and early adult years, and declines thereafter.

**II.Clinical manifestations**

**A.**The intense nasal itching that occurs in allergic rhinitis is associated with nose rubbing, pushing the tip of the nose up with the hand (the “allergic salute”), and a transverse nasal crease.

**B.**Adults and older children frequently have clear mucus. Young children have persistent rhinorrhea and often snort, sniff, cough, and clear their throats. Mouth breathing is common. Allergic rhinitis occurs in association with sinusitis, asthma, eczema and allergic conjunctivitis.

**III.Evaluation**

**A.Nasal examination.** The nasal mucosa frequently displays a pale bluish hue or pallor along with turbinate edema. In nonallergic or vasomotor rhinitis, the nasal turbinates are erythematous and boggy.

**B.Identification of allergens.** For patients in whom symptoms are not well controlled with medications and in whom the cause of rhinitis is not evident from the history, skin testing may provide an in vivo assessment of IgE antibodies.

**C.Skin tests.** Immediate hypersensitivity skin testing is a quick, inexpensive, and safe way to identify the presence of allergen specific IgE.

**IV.Management of allergic rhinitis (rhinosinusitis)**

**A.Allergen identification and avoidance.** The history frequently identifies involvement of pollens, molds, house dust mites and insects, such as fleas and cockroaches, or animal allergens

**B.Allergen avoidance measures:**

**1.**Maintaining the relative humidity at 50 percent or less to limit house dust mite and mold growth and avoiding exposure to irritants, such as cigarette smoke.

**2.**Air conditioners decrease concentrations of pollen, mold, and dust mite allergens in indoor air.

**3.**Avoiding exposure to the feces of the house dust mite is facilitated by removing carpets and furry pets, and washing bedding in hot water once weekly.

**4.**HEPA filters may help reduce animal allergens. Ordinary vacuuming and dusting have little effect.

**C.Pharmacologic treatment**

**1.**Nasal decongestant sprays are not recommended in the treatment of allergic rhinitis. Tachyphylaxis develops after three to seven days, rebound nasal congestion results, and continued use causes rhinitis medicamentosa.

**2.Intranasal corticosteroids.** Topical intranasal steroid therapy is presently the most effective single maintenance therapy for allergic rhinitis and causes few side effects. Topical nasal steroids are more effective than cromolyn and second generation antihistamines. Most studies show no effect on growth at recommended doses.

**a.**The addition of antihistamine or antihistamine-decongestant combination to nasal corticosteroids offers little additional clinical benefit.

**b.**Topical nasal steroids are available in both aqueous and freon-propelled preparations. The aqueous preparations may be particularly useful in patients in whom freon preparations cause mucosal drying, crusting, or epistaxis. Rarely, nasal steroids are associated with nasal septal perforation.

**c.**As needed use appears to be almost as effective as daily use in patients with episodic symptoms.

**d.**The preparations requiring once-daily dosing are preferred. These include triamcinolone, budesonide, fluticasone, or mometasone. Mometasone is approved for use in children older than two years. For children, mometasone (Nasonex) is the preferred as first-line therapy. Budesonide and fluticasone propionate are approved for use in children older than six years.

| Drugs for Allergic Rhinitis | | |
|---|---|---|
| **Drug** | **Trade name** | **Dose** |
| **Corticosteroid Nasal Sprays** | | |
| Triamcinolone | Nasacort | Two sprays qd |
| Budesonide | Rhinocort AQ | Two sprays qd |
| Fluticasone | Flonase | Two sprays qd |
| Mometasone | Nasonex | Two sprays qd |
| Beclomethasone | Beconase<br>Vancenase<br>Beconase AQ<br>Vancenase AQ | One spray two to qid<br>One spray bid-qid<br>One to two sprays bid<br>One to two sprays bid |
| Flunisolide | Nasalide | Two sprays bid |
| **Oral $H_1$-receptor Blockers** | | |
| Citrizine | Zyrtec<br>Zyrtec-D | 5 or 10 mg once/d<br>Cetirizine 5 mg, pseudoephedrine 120 mg; 1 tablet bid |
| Desloratadine | Clarinex | 5 mg once/d |
| Fexofenadine | Allegra | 60 mg bid or 180 mg once/d |
| Loratadine | Claritin<br>Claritin Reditabs<br>Alavert<br>Claritin-D | 10 mg once/d<br><br>Loratadine 5 mg, pseudoephedrine 120 m; 1 tab qAM |
| **Leukotriene Modifier** | | |
| Montelukast | Singulair | 10 mg once/d |

**D. Antihistamines**

**1.** Antihistamines are clearly less effective than topical nasal steroids. Antihistamines typically reduce itching, sneezing, and rhinorrhea, but may not completely eliminate the symptoms of nasal congestion.

**2.** Two second-generation antihistamines are currently available in syrup for young children. Cetirizine (Zyrtec) is approved for children ≥6 months of age. Loratadine (Claritin) is approved for use in children ≥2 years of age and is available over the counter. Second-generation antihistamines and nasal corticosteroids are not approved for children under two and three years of age, respectively. Rondec (carbinoxamine maleate-pseudoephedrine) drops are approved for children one month and older.

**3.** In relieving symptoms, second-generation drugs are less efficacious than corticosteroids and equally or more efficacious than cromolyn. The addition of antihistamines to topical nasal steroids may be useful in patients with concomitant allergic conjunctivitis. Oral antihistamine combinations that contain the decongestant, pseudoephedrine, provide better symptom relief than that associated with antihistamine alone.

**4. Adverse effects.**

**a.** First-generation antihistamines easily cross the blood brain barrier and cause sedation, making them relatively less desirable. Sedation occurs uncommonly with second-generation antihistamines other than cetirizine and azelastine.

**b.** Metabolites of second-generation antihistamines, such as the metabolite of terfenadine, fexofenadine (Allegra), and desloratadine (Clarinex) are classified as "third-generation antihistamines." These compounds avoid potential cardiotoxic effects of the second-generation compounds.

**c.** Cetirizine, fexofenadine, desloratadine, and loratadine have not been associated with QT prolongation. However, coadministration with P450-active drugs increases loratadine levels. In addition, licorice ingestion prolongs QT-intervals and may potentially have additive effects.

**5.** Second-generation antihistamines may be preferable in patients with mild symptoms, or those preferring pills over nose sprays, especially if allergic conjunctivitis is also present. Cetirizine (Zyrtec) is reserved for those who fail loratadine (Claritin) or fexofenadine (Allegra), as cetirizine has sedative properties.

**E. Cromolyn and nedocromil** decrease allergic inflammation by inhibiting mast cell mediator release. Cromolyn, but not nedocromil, is available in the United States. Cromolyn is less effective than topical nasal steroids.

**F. Allergen immunotherapy**

**1.** Allergen immunotherapy involves the subcutaneous administration of increasing doses of therapeutic vaccines of allergens.

**2. Efficacy.** Allergen immunotherapy to tree, grass and ragweed pollens, Alternaria mold and house dust mite is efficacious in allergic rhinitis. Immunotherapy should be considered in patients in whom pharmacotherapy and avoidance of allergens have failed to resolve symptoms.

**References:** See page 255.

# Allergic Conjunctivitis

Allergic conjunctivitis is estimated to affect 20 percent of the population on an annual basis. Allergic conjunctivitis is associated with itching, tearing, redness, burning, photophobia, and mucus discharge.

**I.Pathophysiology**

**A.**Allergic conjunctivitis has an average age of onset of 20 years of age, and is principally a disease of young adults. Symptoms tend to decrease with age.

**B.Acute allergic conjunctivitis** is an acute, hypersensitivity reaction caused by environmental exposure to allergens. It is characterized by intense episodes of itching, hyperemia, tearing, chemosis, and eyelid edema. It resolves in less than 24 hours.

**C.Seasonal allergic conjunctivitis** (SAC) is also known as allergic conjunctivitis. It is frequently associated with rhinitis. It occurs in the spring and late summer, and it is caused by exposure to pollen, grasses, and ragweed.

**D.Perennial allergic conjunctivitis** (PAC) is a mild, chronic, allergic conjunctivitis related to environmental exposure to year-round allergens such as dust mites and mold.

**E.**Acute allergic conjunctivitis, seasonal allergic conjunctivitis (SAC), and perennial allergic conjunctivitis (PAC) are referred to as "allergic conjunctivitis," and result from allergens.

**II.Clinical evaluation**

**A.**Allergic conjunctivitis is frequently associated with atopy, allergic rhinitis, skin allergies, and asthma.

**B.Signs and symptoms of allergic conjunctivitis** include itching, tearing, conjunctival edema, hyperemia, eyelid edema, watery discharge, burning, and photophobia. Symptoms are usually bilateral. The differential diagnosis includes infectious conjunctivitis, blepharitis, and dry eye.

**C.**Acute allergic conjunctivitis occurs rapidly upon exposure to an allergen, such as cat dander. Symptoms can be severe and debilitating but resolve quickly, usually within 24 hours of removal of the allergen. Seasonal allergic conjunctivitis typically has a less dramatic onset; it will have a more predictable and chronic course that corresponds to the ragweed (late summer and early fall), grass (summer), and pollen (spring) seasons.

**D.Laboratory findings.** The diagnosis of allergic conjunctivitis is usually made clinically; therefore, laboratory testing is not typically performed.

**III.Treatment of allergic conjunctivitis**

**A.**Avoidance of the allergen is recommended. Preventive steps to reduce symptoms of SAC include limiting outdoor exposure during high "counts" of pollen and ragweed, use of air conditioning, and keeping windows closed. For those with PAC, prevention includes replacement of old pillows and mattresses, covers for pillows and mattresses, frequent washing of beddings, reducing humidity, and frequent vacuuming and dusting. Old curtains or drapes should be removed. When the allergen is animal dander, the animal may need to be removed from the home.

**B.**In all types of allergic conjunctivitis, patients should not rub their eyes because that can cause mast cell degranulation. Patients should use topical antihistamines, frequent artificial tears, and cool compresses.

**C.Mast cell stabilizers**

**1.**Mast cell stabilizers include Crolom (cromolyn 4.0 percent), Opticrom (cromolyn), and Alomide (lodoxamide). These drugs are particularly useful for allergic conjunctivitis. Dosing is four times per day. Since the onset of action is 5 to 14 days after therapy has been initiated, these medicines are not useful for acute conjunctivitis. These drops cause burning and stinging.

**2.**These drugs are well tolerated, non-toxic, and can be used in contact lens wearers. However disadvantages include delayed onset of action, maintenance therapy, and multiple daily dosing.

**D.Antihistamines**

**1.Oral antihistamines** and combinations of antihistamines plus decongestants include Allegra (fexofenadine, 60 mg bid or tab ER: 180 mg qd), Allegra D (fexofenadine plus pseudoephedrine, 1 tab bid), Claritin (loratadine, 10 mg qd), Claritin-D (loratadine plus pseudoephedrine, 1 tab qd), and Zyrtec (cetirizine, 5-10 mg qd) or Zyrtec-D (cetirizine plus pseudoephedrine, 1 tab bid).

**2.**The full effect of oral administration of antihistamines occurs hours after initiating therapy. Since oral antihistamine use is associated with drying of mucosal membranes, the use of oral antihistamines may worsen allergic symptoms. This effect is not observed with topical antihistamines.

**3.Topical antihistamines** include Emadine (emedastine) and Livostin (levocabastine), which are used as one drop up to 4 times daily. The advantages of topical antihistamine usage include a more rapid onset of action and reduced drowsiness and dry eyes. Emadine and Livostin are topical, highly specific, H1-receptor antagonists, and their onset of action is within minutes.

**4.Topical, antihistamine/vasoconstrictor combinations** have been shown to be effective. Examples of such combination drugs include Naphcon-A (naphazoline/pheniramine), Vasocon-A (naphazoline/pheniramine), OcuHist (naphazoline/pheniramine), and Opcon-A (naphazoline/pheniramine). Dosing is up to four times daily. However, chronic use can lead to rebound hyperemia.

**5.Olopatadine (Patanol)** is a combination antihistamine and mast cell stabilizer. It is the most commonly prescribed drug for allergic conjunctivitis. The H1-

receptor selectivity is superior to that of other antihistamines. Patanol is very safe and effective. Side effects include stinging and headache. Dosing is two to four times daily.

**E.Corticosteroids**

**1.**Topical corticosteroid use should only be used for short "pulse therapy" when antihistamines and mast cell stabilizers provide inadequate therapy. Side effects from corticosteroids include cataract formation, elevated intraocular pressure (IOP), glaucoma, and secondary infections. Ocular steroids should only be administered by ophthalmologists.

**2.**Prednisolone and dexamethasone have the greatest risk of raising IOP. "Soft" steroids are a group of topical corticosteroids that have a greatly reduced risk of causing increased IOP, since they undergo rapid inactivation upon penetration of the cornea. These drugs include Pred Mild (prednisolone), FML (fluoromethalone), HMS (medrysone), Lotemax (loteprednol), and Vexol (rimexolone). They are administered two to four times per day for two weeks.

**F.Treatment recommendations**

**1.Acute allergic conjunctivitis**

**a.**Topical antihistamine/vasoconstrictors are usually sufficient in treating short exacerbations of symptoms. Combination drugs include Naphcon-A (naphazoline/pheniramine), Vasocon-A (naphazoline/pheniramine), OcuHist (naphazoline/pheniramine), and Opcon-A (naphazoline/pheniramine). Dosing is up to four times daily. Chronic use (greater than two weeks) can lead to rebound hyperemia.

**b.**For frequent attacks of acute allergic conjunctivitis (occurring more than two days per month), mast cell stabilizers can be added. Olopatadine (Patanol), a combination drug consisting of an antihistamine and mast cell stabilizer, is a good agent for treating more frequent attacks. It can be used up to four times per day.

**c.**If these are ineffective, oral antihistamines may be helpful. Oral antihistamines and combinations of antihistamines plus decongestants include Allegra (fexofenadine, 60 mg bid or tab ER: 180 mg qd), Allegra D (fexofenadine plus pseudoephedrine, 1 tab bid), Claritin (loratadine, 10 mg qd), Claritin-D (loratadine plus pseudoephedrine, 1 tab qd), and Zyrtec (cetirizine, 5-10 mg qd) or Zyrtec-D (cetirizine plus pseudoephedrine, 1 tab bid). Frequent use of artificial tears is recommended while using oral antihistamines.

**2.Seasonal allergic conjunctivitis and perennial allergic conjunctivitis**

**a.Olopatadine (Patanol)** should be initiated two weeks before the onset of symptoms is anticipated. Patanol, a combination mast cell stabilizer and antihistamine, has become the first-line drug of choice in treating SAC and PAC. It is approved for children older than five years of age and adults. Dosing is two to four times daily.

**b.**Oral antihistamines may be helpful; however, these agents cause decreased tear production. These patients are frequently using oral antihistamines for systemic symptoms; therefore, artificial tears should be used.

**c.**A short two-week course of topical steroids can be helpful in resistant cases. Pred Mild (prednisolone), FML (fluoromethalone), HMS (medrysone), Lotemax (loteprednol), or Vexol (rimexolone) are administered two to four times per day for two to three weeks.

**References: See page 255.**

# Acute Bronchitis

Acute bronchitis is one of the most common diagnoses in ambulatory care medicine, accounting for 2.5 million physician visits per year. This condition is one of the top 10 diagnoses for which patients seek medical care. Acute bronchitis is one of the most common diagnoses made by primary care physicians. Viruses are the most common cause of acute bronchitis in otherwise healthy adults. Only a small portion of acute bronchitis infections are caused by nonviral agents, with the most common organisms being *Mycoplasma pneumoniae and Chlamydia pneumoniae*.

**I.Diagnosis**

**A.**The cough in acute bronchitis may produce either clear or purulent sputum. This cough generally lasts seven to 10 days. Approximately 50 percent of patients with acute bronchitis have a cough that lasts up to three weeks, and 25 percent of patients have a cough that persists for over a month.

**B.Physical examination.** Wheezing, rhonchi, or a prolonged expiratory phase may be present.

**C.Diagnostic studies**

**1.**The appearance of sputum is not predictive of whether a bacterial infection is present. Purulent sputum is most often caused by viral infections. Microscopic examination or culture of sputum generally is not helpful. Since most cases of acute bronchitis are caused by viruses, cultures are usually negative or exhibit normal respiratory flora. M. pneumoniae or C. pneumoniae infection are not detectable on routine sputum culture.

**2.**Acute bronchitis can cause transient pulmonary function abnormalities which resemble asthma. Therefore, to diagnose asthma, changes that persist after the acute phase of the illness must be documented. When pneumonia is suspected, chest radiographs and pulse oximetry may be helpful.

## II.Pathophysiology

| Selected Triggers of Acute Bronchitis |
|---|
| Viruses: adenovirus, coronavirus, coxsackievirus, enterovirus, influenza virus, parainfluenza virus, respiratory syncytial virus, rhinovirus<br>Bacteria: *Bordetella pertussis, Bordetella parapertussis, Branhamella catarrhalis, Haemophilus influenzae, Streptococcus pneumoniae,* atypical bacteria<br>(eg, *Mycoplasma pneumoniae, Chlamydia pneumoniae,* Legionella species)<br>Yeast and fungi: *Blastomyces dermatitidis, Candida albicans, Candida tropicalis, Coccidioides immitis, Cryptococcus neoformans, Histoplasma capsulatum*<br>Noninfectious triggers: asthma, air pollutants, ammonia, cannabis, tobacco, trace metals, others |

**A.**Acute bronchitis is usually caused by a viral infection. In patients younger than one year, respiratory syncytial virus, parainfluenza virus, and coronavirus are the most common isolates. In patients one to 10 years of age, parainfluenza virus, enterovirus, respiratory syncytial virus, and rhinovirus predominate. In patients older than 10 years, influenza virus, respiratory syncytial virus, and adenovirus are most frequent.

**B.**Parainfluenza virus, enterovirus, and rhinovirus infections most commonly occur in the fall. Influenza virus, respiratory syncytial virus, and coronavirus infections are most frequent in the winter and spring.

## III.Signs and symptoms

**A.**Cough is the most commonly observed symptom of acute bronchitis. The cough begins within two days of infection in. Most patients have a cough for less than two weeks; however, 26 percent are still coughing after two weeks, and a few cough for six to eight weeks**.**

**B.**Other signs and symptoms may include sputum production, dyspnea, wheezing, chest pain, fever, hoarseness, malaise, rhonchi, and rales. Sputum may be clear, white, yellow, green, or tinged with blood. Color alone should not be considered indicative of bacterial infection.

## IV.Physical examination and diagnostic studies

**A.**The physical examination should focus on fever, tachypnea, wheezing, rhonchi, and prolonged expiration. Evidence of consolidation is absent. Fever may be present in some patients with acute bronchitis. However, high fever should prompt consideration of pneumonia or influenza.

**B.**Chest radiography should be reserved for patients with possible pneumonia, heart failure, advanced age, chronic obstructive pulmonary disease, malignancy, tuberculosis, or immunocompromised or debilitated status.

## V.Differential diagnosis

**A.**Acute bronchitis or pneumonia can present with fever, constitutional symptoms and a productive cough. Patients with pneumonia often have rales. When pneumonia is suspected on the basis of the presence of a high fever, constitutional symptoms or severe dyspnea, a chest radiograph should be obtained.

**Differential Diagnosis of Acute Bronchitis**

| Disease process | Signs and symptoms |
|---|---|
| Asthma | Evidence of reversible airway obstruction even when not infected |
| Allergic aspergillosis | Transient pulmonary infiltrates<br>Eosinophilia in sputum and peripheral blood smear |
| Occupational exposures | Symptoms worse during the work week but tend to improve during weekends, holidays and vacations |
| Chronic bronchitis | Chronic cough with sputum production on a daily basis for a minimum of three months<br>Typically occurs in smokers |
| Sinusitis | Tenderness over the sinuses, postnasal drainage |
| Common cold | Upper airway inflammation and no evidence of bronchial wheezing |
| Pneumonia | Evidence of infiltrate on the chest radiograph |
| Congestive heart failure | Basilar rales, orthopnea<br>Cardiomegaly<br>Evidence of increased interstitial or alveolar fluid on the chest radiograph<br>$S_3$ gallop, tachycardia |
| Reflux esophagitis | Intermittent symptoms worse when lying down<br>Heartburn |
| Bronchogenic tumor | Constitutional signs often present<br>Cough chronic, sometimes with hemoptysis |
| Aspiration syndromes | Usually related to a precipitating event, such as smoke inhalation<br>Vomiting<br>Decreased level of consciousness |

**B.Asthma** should be considered in patients with repetitive episodes of acute bronchitis. Patients who repeatedly present with cough and wheezing can be given spirometric testing with bronchodilation to help differentiate asthma from recurrent bronchitis.

**C.Congestive heart failure** may cause cough, shortness of breath and wheezing in older patients. Reflux esophagitis with chronic aspiration can cause bronchial inflammation with cough and wheezing. Bronchogenic tumors may produce a cough and obstructive symptoms.

**VI.Treatment**

**A.Protussives and antitussives**

**1.**Because acute bronchitis is most often caused by a viral infection, usually only symptomatic treatment is required. Treatment can focus on preventing or controlling the cough (antitussive therapy).

**2.**Antitussive therapy is indicated if cough is creating significant discomfort. Studies have reported success rates ranging from 68 to 98 percent. Nonspecific antitussives, such as hydrocodone (Hycodan), dextromethorphan (Delsym), codeine (Robitussin A-C), carbetapentane (Rynatuss), and benzonatate (Tessalon), simply suppress cough.

***Selected Nonspecific Antitussive Agents***

| Preparation | Dosage | Side effects |
|---|---|---|
| Hydromorphone-guaifenesin (Hycotuss) | 5 mg per 100 mg per 5 mL (one teaspoon) | Sedation, nausea, vomiting, respiratory depression |
| Dextromethorphan (Delsym) | 30 mg every 12 hours | Rarely, gastrointestinal upset or sedation |
| Hydrocodone (Hycodan syrup or tablets) | 5 mg every 4 to 6 hours | Gastrointestinal upset, nausea, drowsiness, constipation |
| Codeine (Robitussin A-C) | 10 to 20 mg every 4 to 6 hours | Gastrointestinal upset, nausea, drowsiness, constipation |
| Carbetapentane (Rynatuss) | 60 to 120 mg every 12 hours | Drowsiness, gastrointestinal upset |
| Benzonatate (Tessalon) | 100 to 200 mg three times daily | Hypersensitivity, gastrointestinal upset, sedation |

**B.Bronchodilators.** Patients with acute bronchitis who used an albuterol metered-dose inhaler are less likely to be coughing at one week, compared with those who received placebo.

**C.Antibiotics**. Physicians often treat acute bronchitis with antibiotics, even though scant evidence exists that antibiotics offer any significant advantage over placebo. Antibiotic therapy is beneficial in patients with exacerbations of chronic bronchitis.

**Oral Antibiotic Regimens for Bronchitis**

| Drug | Recommended regimen |
|---|---|
| Azithromycin (Zithromax) | 500 mg; then 250 mg qd |
| Erythromycin | 250-500 mg q6h |
| Clarithromycin (Biaxin) | 500 mg bid |
| Levofloxacin (Levaquin) | 500 mg qd |
| Trovafloxacin (Trovan) | 200 mg qd |
| Trimethoprim/sulfamethoxazole (Bactrim, Septra) | 1 DS tablet bid |
| Doxycycline | 100 mg bid |

**D.Bronchodilators**. Significant relief of symptoms occurs with inhaled albuterol (two puffs four times daily). When productive cough and wheezing are present, bronchodilator therapy may be useful.

**References:** See page 255.

# Asthma

Asthma is the most common chronic disease among children. Asthma triggers include viral infections; environmental pollutants, such as tobacco smoke; aspirin, nonsteroidal anti-inflammatory drugs, and sustained exercise, particularly in cold environments.

**I.Diagnosis**

**A.**Symptoms of asthma may include episodic complaints of breathing difficulties, seasonal or nighttime cough, prolonged shortness of breath after a respiratory infection, or difficulty sustaining exercise.

**B.**Wheezing does not always represent asthma. Wheezing may persist for weeks after an acute bronchitis episode. Patients with chronic obstructive pulmonary disease may have a reversible component superimposed on their fixed obstruction. Etiologic clues include a personal history of allergic disease, such as rhinitis or atopic dermatitis, and a family history of allergic disease.

**C.**The frequency of daytime and nighttime symptoms, duration of exacerbations and asthma triggers should be assessed.

**D.Physical examination.** Hyperventilation, use of accessory muscles of respiration, audible wheezing, and a prolonged expiratory phase are common. Increased nasal secretions or congestion, polyps, and eczema may be present.

**E.Measurement of lung function.** An increase in the forced expiratory volume in one second ($FEV_1$) of 12% after treatment with an inhaled beta$_2$ agonist is sufficient to make the diagnosis of asthma. A 12% change in peak expiratory flow rate (PEFR) measured on a peak-flow meter is also diagnostic.

## II. Treatment of asthma

### A. Beta$_2$ agonists

**1.** Inhaled short-acting beta$_2$-adrenergic agonists are the most effective drugs available for treatment of acute bronchospasm and for prevention of exercise-induced asthma. Levalbuterol (Xopenex), the R-isomer of racemic albuterol, offers no significant advantage over racemic albuterol.

**2.Salmeterol (Serevent)**, a long-acting beta$_2$ agonist, has a relatively slow onset of action and a prolonged effect.

**a.** Salmeterol should not be used in the treatment of acute bronchospasm. Patients taking salmeterol should use a short-acting beta$_2$ agonist as needed to control acute symptoms. Twice-daily inhalation of salmeterol has been effective for maintenance treatment in combination with inhaled corticosteroids.

**b.** Fluticasone/Salmeterol (Advair Diskus) is a long-acting beta agonist and corticosteroid combination; dry-powder inhaler [100, 250 or 500 µg/puff],1 puff q12h.

**3.Formoterol (Foradil)** is a long-acting beta$_2$ agonist like salmeterol. It should only be used in patients who already take an inhaled corticosteroid. Patients taking formoterol should use a short-acting beta$_2$ agonist as needed to control acute symptoms. For maintenance treatment of asthma in adults and children at least 5 years old, the recommended dosage is 1 puff bid.

**4.Adverse effects of beta$_2$ agonists.** Tachycardia, palpitations, tremor and paradoxical bronchospasm can occur. High doses can cause hypokalemia.

**Drugs for Asthma**

| Drug | Formulation | Dosage |
|---|---|---|
| **Inhaled beta$_2$-adrenergic agonists, short-acting** | | |
| Albuterol<br>*Proventil*<br>*Proventil-HFA*<br>*Ventolin*<br>*Ventolin*<br>*Rotacaps* | metered-dose inhaler (90 µg/puff)<br><br>dry-powder inhaler (200 µg/inhalation) | 2 puffs q4-6h PRN<br><br>1-2 capsules q4-6h PRN |
| Albuterol<br>*Proventil*<br>multi-dose vials<br>*Ventolin Nebules*<br>*Ventolin* | nebulized | 2.5 mg q4-6h PRN |
| Levalbuterol -<br>*Xopenex* | nebulized | 0.63-1.25 mg q6-8h PRN |
| **Inhaled beta2-adrenergic agonist, long-acting** | | |
| Formoterol -<br>*Foradil* | dry-powder inhaler (12 µg/puff) | 1 puff bid. |
| Salmeterol<br>*Serevent*<br>*Serevent Diskus* | metered-dose inhaler (21 µg/puff)<br>dry-powder inhaler (50 µg/inhalation) | 2 puffs q12h<br><br>1 inhalation q12h |
| **Fluticasone/Salmeterol** *Advair Diskus* | dry-powder inhaler (100, 250 or 500 µg/puff) | 1 puff q12h |
| **Inhaled Corticosteroids** | | |
| Beclomethasone dipropionate<br>*Beclovent*<br>*Vanceril*<br>Vanceril Double-Strength | metered-dose inhaler (42 µg/puff) (84 µg/puff) | 4-8 puffs bid<br><br>2-4 puffs bid |
| Budesonide<br>*Pulmicort*<br>*Turbuhaler* | dry-powder inhaler (200 µg/inhalation) | 1-2 inhalations bid |
| Flunisolide -<br>*AeroBid* | metered-dose inhaler<br>(250 µg/puff) | 2-4 puffs bid |
| Fluticasone<br>Flovent<br><br>*Flovent Rotadisk* | metered-dose inhaler (44, 110 or 220 µg/puff)<br>dry-powder inhaler (50, 100 or 250 µg/inhalation) | 2-4 puffs bid (44 µg/puff)<br>1 inhalation bid (100 µg/inhalation) |
| Triamcinolone acetonide<br>*Azmacort* | metered-dose inhaler (100 µg/puff) | 2 puffs tid-qid or 4 puffs bid |

| Drug | Formulation | Dosage |
|---|---|---|
| **Leukotriene Modifiers** | | |
| Montelukast - *Singulair* | tablets | 10 mg qhs |
| Zafirlukast - *Accolate* | tablets | 20 mg bid |
| Zileuton - *Zyflo* | tablets | 600 mg qid |
| **Mast Cell Stabilizers** | | |
| Cromolyn *Intal* | metered-dose inhaler (800 µg/puff) | 2-4 puffs tid-qid |
| Nedocromil *Tilade* | metered-dose inhaler (1.75 mg/puff) | 2-4 puffs bid-qid |
| **Phosphodiesterase Inhibitor** | | |
| **Theophylline** *Slo-Bid Gyrocaps*, *Theo-Dur*, *Unidur* | extended-release capsules or tablets | 100-300 mg bid |

**B.Inhaled corticosteroids**

**1.**Regular use of an inhaled corticosteroid can suppress inflammation, decrease bronchial hyperresponsiveness and decrease symptoms. Inhaled corticosteroids are recommended for most patients.

**2.Adverse effects.** Inhaled corticosteroids are usually free of toxicity. Dose-dependent slowing of linear growth may occur within 6-12 weeks in some children. Decreased bone density, glaucoma and cataract formation have been reported. Churg-Strauss vasculitis has been reported rarely. Dysphonia and oral candidiasis can occur. The use of a spacer device and rinsing the mouth after inhalation decreases the incidence of candidiasis.

**C.Leukotriene modifiers**

**1.**Leukotrienes increase production of mucus and edema of the airway wall, and may cause bronchoconstriction. Montelukast and zafirlukast are leukotriene receptor antagonists. Zileuton inhibits synthesis of leukotrienes.

**2.Montelukast (Singulair)** is modestly effective for maintenance treatment of intermittent or persistent asthma. It is taken once daily in the evening. It is less effective than inhaled corticosteroids, but addition of montelukast may permit a reduction in corticosteroid dosage. Montelukast added to oral or inhaled corticosteroids can improve symptoms.

**3.Zafirlukast (Accolate)** is modestly effective for maintenance treatment of mild-to-moderate asthma It is less effective than inhaled corticosteroids. Taking zafirlukast with food markedly decreases its bioavailability. Theophylline can decrease its effect. Zafirlukast increases serum concentrations of oral anticoagulants and may cause bleeding. Infrequent adverse effects include mild headache, gastrointestinal disturbances and increased serum aminotransferase activity. Drug-induced lupus and Churg-Strauss vasculitis have been reported.

**4.Zileuton (Zyflo)** is modestly effective for maintenance treatment, but it is taken four times a day and patients must be monitored for hepatic toxicity.

**D.Cromolyn (Intal) and nedocromil (Tilade)**

**1.**Cromolyn sodium, an inhibitor of mast cell degranulation, can decrease airway hyperresponsiveness in some patients with asthma. The drug has no bronchodilating activity and is useful only for prophylaxis. Cromolyn has virtually no systemic toxicity.

**2.**Nedocromil has similar effects as cromolyn. Both cromolyn and nedocromil are much less effective than inhaled corticosteroids.

**E.Theophylline**

**1.**Oral theophylline has a slower onset of action than inhaled $beta_2$ agonists and has limited usefulness for treatment of acute symptoms. It can, however, reduce the frequency and severity of symptoms, especially in nocturnal asthma, and can decrease inhaled corticosteroid requirements.

**2.**When theophylline is used alone, serum concentrations between 8-12 mcg/mL provide a modest improvement is $FEV_1$. Serum levels of 15-20 mcg/mL are only minimally more effective and are associated with a higher incidence of cardiovascular adverse events.

**F.Oral corticosteroids** are the most effective drugs available for acute exacerbations of asthma unresponsive to bronchodilators.

**1.**Oral corticosteroids decrease symptoms and may prevent an early relapse. Chronic use of oral corticosteroids can cause glucose intolerance, weight gain, increased blood pressure, osteoporosis, cataracts, immunosuppression and decreased growth in children. Alternate-day use of corticosteroids can decrease the incidence of adverse effects, but not of osteoporosis.

**2.Prednisone, prednisolone or methylprednisolone** (Solu-Medrol), 40-60 mg qd; for children, 1-2 mg/kg/day to a maximum of 60 mg/day. Therapy is continued for 3-10 days. The oral steroid dosage does not need to be tapered after short-course "burst" therapy if the patient is receiving inhaled steroid therapy.

| Pharmacotherapy for Asthma Based on Disease Classification | | |
|---|---|---|
| **Classification** | **Long-term control medications** | **Quick-relief medications** |
| Mild intermittent | | Short-acting beta$_2$ agonist as needed |
| Mild persistent | Low-dose inhaled corticosteroid or cromolyn sodium (Intal) or nedocromil (Tilade) | Short-acting beta$_2$ agonist as needed |
| Moderate persistent | Medium-dose inhaled corticosteroid plus a long-acting bronchodilator (long-acting beta$_2$ agonist) | Short-acting beta$_2$ agonist as needed |
| Severe persistent | High-dose inhaled corticosteroid plus a long-acting bronchodilator and systemic corticosteroid | Short-acting beta$_2$ agonist as needed |

**III.Management of acute exacerbations**

**A.**High-dose, short-acting beta$_2$ agonists delivered by a metered-dose inhaler with a volume spacer or via a nebulizer remains the mainstay of urgent treatment.

**B.**Most patients require therapy with systemic corticosteroids to resolve symptoms and prevent relapse. Hospitalization should be considered if the PEFR remains less than 70% of predicted. Patients with a PEFR less than 50% of predicted who exhibit an increasing $pCO_2$ level and declining mental status are candidates for intubation.

**C.**Non-invasive ventilation with bilevel positive airway pressure (BIPAP) may be used to relieve the work-of-breathing while awaiting the effects of acute treatment, provided that consciousness and the ability to protect the airway have not been compromised.

**References:** See page 255.

# Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is characterized by the presence of persistent airflow limitation, arising usually after many years of tobacco smoking. This disease affects at least 6% of men and 3% of women.

**I.Characteristics of COPD**

**A.Chronic bronchitis** is characterized by a cough that produces sputum and that lasts at least 3 months per year for at least 2 consecutive years. Emphysema refers to enlargement and destruction of the air spaces in the lungs. The term "COPD" describes any combination of chronic bronchitis and emphysema.

**B.Causes.** The principal risk factor for development of COPD is smoking. About 15% of smokers develop COPD.

**C.**Clinical clues to COPD include history of smoking greater than 20 pack-years, older age at onset of symptoms (usually >60 years), a negative allergy history, no family history of asthma, and a slowly progressive rate of disease.

| Classification of acute exacerbations of COPD |
|---|
| **Type I**<br>One of three cardinal symptoms:<br>1. Worsening dyspnea<br>2. Increase in sputum purulence<br>3. Increase in sputum volume<br>and<br>**One of the following:**<br>Upper respiratory tract infection in the past 5 days<br>Fever without other apparent cause<br>Increased wheezing<br>Increased cough<br>Increase in respiratory or heart rate by 20% above baseline |
| **Type II**<br>Two of three cardinal symptoms |
| **Type III**<br>All three cardinal symptoms |

**II.Diagnostic testing**

**A.Pulse oximetry** is an inexpensive, noninvasive procedure for assessing oxygen saturation.

**B.Arterial blood gases.** Both hypercarbia and hypoxemia occur when pulmonary function falls to below 25-30% of the predicted normal value.

**C.Pulmonary function testing** is a useful means for assessing ventilatory function. Irreversible airflow limitation, or the reduced ratio of forced expiratory volume in 1 second ($FEV_1$) to forced vital capacity (FVC), is the hallmark of COPD. Emphysema manifests as low carbon monoxide diffusion capacity with hyperinflation (increased total lung capacity) and increased residual volume. Peak-flow meters are available that can provide a quick assessment of expiratory function.

**D.Chest radiography** will permit identification of patients with COPD with pneumonia, pneumothorax, and decompensated CHF.

**E.An ECG** may be useful in patients who have a history of chest pain, syncope, and palpitations.

**F.Labs:** Complete blood count (CBC) is useful in patients with acute exacerbation of COPD if pneumonia is suspected. The hematocrit is frequently elevated as a result of chronic hypoxemia.

**III.Treatment**

**Stepwise treatment of chronic obstructive pulmonary disease**

| Indication | Intervention |
|---|---|
| Known diagnosis | Smoking cessation, vaccinations Nicotine replacement therapy or bupropion (Zyban) |
| Mild, intermittent symptoms | Short-acting anticholinergic or beta$_2$ agonist prn |
| Regular symptoms | Regular use of ipratropium (Atrovent), 2-4 inhalations tid to qid prn, or albuterol, 2-4 inhalations tid to qid prn The ipratropium (Atrovent) inhalation dose is 500 mcg/2.5 mL solution nebulized 3-4 times daily. |
| Symptoms continue or are nocturnal | Add salmeterol (Serevent), 25 micrograms/dose, 2 inhalations bid. Not to be used for rescue |
| Symptoms continue | Sustained-release theophylline 400-800 mg/day. Low therapeutic level (ie, 55-85 micromoles/L) |
| Symptoms continue | Fluticasone (Flovent), 2 puffs bid. Only if objective improvement after 2-wk course of oral corticosteroids |
| Moderate to severe disease | Oxygen therapy 24 hr/day. If PO2 <55 mm Hg or <60 mm Hg with evidence of cor pulmonale, polycythemia, or nocturnal or exertional desaturation |

**A.**Bronchodilators improve the airway obstruction of COPD and decrease breathlessness. Short-acting bronchodilators include anticholinergic agents (eg, ipratropium bromide [Atrovent]) and beta$_2$ agonists (eg, albuterol, terbutaline sulfate [Brethaire, Brethine, Bricanyl]).

**B.**While beta$_2$ agonists are the bronchodilators of choice in asthma, elderly patients with COPD tend to have a greater response to anticholinergic drugs. A combination of both agents has greater bronchodilator benefit than single-agent therapy. COPD patients are likely to require larger doses of bronchodilating drugs than are asthma patients. A typical effective regimen is ipratropium, 4 puffs administered with a spacer four times a day.

**C.**Longer-acting beta$_2$ agonists (eg, formoterol [Foradil], salmeterol [Serevent]) may be of benefit to selected COPD patients.

**D.**A minority of the COPD population (10% to 20%) benefits from inhaled corticosteroids, as determined by $FEV_1$ response to a 2-week trial of oral prednisone, 0.5 mg/kg/day. Patients who respond should be treated with fluticasone.

**1.Fluticasone (Flovent)** 2 puffs bid; inhaler: 44, 110, 220 mcg/puff. Diskus inh: 50, 100, 250 mcg.

**2.Triamcinolone (Azmacort)** MDI 2-4 puffs bid.

**3.Flunisolide (AeroBid, AeroBid-M)** MDI 2-4 puffs bid.

**4.Beclomethasone (Beclovent)** MDI 2-4 puffs bid.

**5.Budesonide (Pulmicort)** MDI 2 puffs bid.

**E.Theophylline** is not widely used because of the potential toxicity of the drug. However, theophylline can be effective at lower doses and serum levels of 55 to 85 micromoles/L. It is most useful in symptomatic patients who have not responded well to the first- and second-line agents. The dosage of long-acting theophylline (Slo-bid, Theo-Dur) is 200-300 mg bid. Theophylline preparations with 24-hour action may be administered once a day in the early evening. Theo-24, 100-400 mg qd [100, 200, 300, 400 mg].

**F.Pneumococcal and influenza vaccination** are recommended for all COPD patients. Both vaccines can be given at the same time at different sites.

**G.Treatment of exacerbations**

**1.Oxygen.** Patients in respiratory distress should receive supplemental oxygen therapy. Oxygen therapy usually is initiated by nasal cannula to maintain an $O_2$ saturation greater than 90%. Patients with hypercarbia may require controlled oxygen therapy using a Venturi mask.

**2.Antibiotics** are indicated when two of three typical symptoms are present: (1) increased sputum volume, (2) increased sputum purulence, and (3) increased dyspnea. Between 25% and 50% of exacerbations are caused by viruses, and the remainder are caused by bacteria. The primary bacterial pathogens are Haemophilus influenzae, Streptococcus pneumoniae, and Moraxella catarrhalis.

**3.Amoxicillin-resistant, beta-lactamase-producing H. influenzae** are common. Azithromycin has an appropriate spectrum of coverage. Levofloxacin is advantageous when gram-negative bacteria or atypical organisms predominate. Amoxicillin-clavulanate has activity against beta-lactamase-producing H. influenzae and M. catarrhalis.

**4.Patients with severe underlying lung disease.** Use of second-line agents (ie, amoxicillin and clavulanate [Augmentin], ciprofloxacin [Cipro], azithromycin [Zithromax]) significantly reduces the treatment failure rate and increases time between exacerbations.

**5.**Seven to 10 days of antibiotic therapy should be sufficient in the absence of pneumonia.

| **Choice of empirical antibiotic therapy for COPD exacerbation** | |
|---|---|
| **First-line treatment** | **Dosage*** |
| Amoxicillin (Amoxil, Trimox, Wymox) | 500 mg tid |
| Trimethoprim-sulfamethoxazole (Bactrim, Cotrim, Septra) | 1 tablet (80/400 mg) bid |
| Doxycycline | 100 mg bid |
| Erythromycin | 250-500 mg qid |
| **Second-line treatment**** | |
| Amoxicillin and clavulanate (Augmentin) | 500-875 mg bid |
| Second- or third-generation cephalosporin (eg, cefuroxime [Ceftin]) | 250-500 mg bid |
| **Macrolides** | |
| Clarithromycin (Biaxin) | 250-500 mg bid |
| Azithromycin (Zithromax) | 500 mg on day 1, then 250 mg qd X 4 days |
| **Quinolones** | |
| Ciprofloxacin (Cipro) | 500-750 mg bid |
| Levofloxacin (Levaquin)*** | 500 mg qd |

*May need adjustment in patients with renal or hepatic insufficiency.
**For patients in whom first-line therapy has failed and those with moderate to severe disease or resistant or gram-negative pathogens.
***Although the newer quinolones have better activity against *Streptococcus pneumoniae,* ciprofloxacin may be preferable in patients with gram-negative organisms.

**H.Methylprednisolone (Solumedrol)**, 125 mg IV every 6 hours for 3 days, followed by prednisone tapered over 2 weeks results in a shortened hospital stay (1 day) and lower rates of treatment failure. Prednisone at a dosage of 40 mg per day for 10 days or less is recommended. Hyperglycemia is the most common adverse effect associated with corticosteroid administration. Inhaled corticosteroids are not beneficial in acute exacerbations of COPD.

**I.Management of acute respiratory failure**

**1.**Acute respiratory failure is manifested by an arterial $PO_2$ of less than 50 mm Hg while breathing room air or a $PCO_2$ of more than 50 mm Hg with a pH of less than 7.35, or both. Oxygen is the cornerstone of therapy in hypoxemic patients. Excessive supplemental oxygen may result in hypercapnia due to suppression of the hypoxic ventilatory drive.

**2.**Arterial blood gases should be monitored in patients given supplemental oxygen for acute exacerbation. Oxygen should be administered by Venturi mask at a concentration of 24-28% or by nasal cannula at low flow rates (1 to 2 L/min) to achieve an arterial $P_O$, of 60 mm Hg with an oxygen saturation of 90-92%.

**3.**Indications for mechanical ventilation in patients with exacerbations of COPD include labored breathing with respiratory rates of more than 30 breaths per minute, moderate to severe respiratory acidosis (pH <7.25-7.30), decreased level of consciousness, respiratory arrest, and complicating comorbid conditions (eg, shock, sepsis, metabolic abnormalities).

**4.Noninvasive positive pressure ventilation (NIPPV)**, administered by tight-fitting mask, is highly effective. NIPPV should not be used in patients who have respiratory arrest, impaired mental status, or copious secretions or those who are at high risk for aspiration.

**5.Invasive mechanical ventilation** is indicated in patients in whom NIPPV fails and in those with obtundation, an inability to clear copious secretions, life-threatening acidosis, or cardiovascular instability.

**J.Surgery.** Lung volume reduction surgery restores chest wall mechanics, improves lung elastic recoil and airflow, and improves oxygen levels. Transplantation may be considered when other therapeutic options have been exhausted, the FEV1 is less than 25% of predicted.

**K.Supplemental oxygen** is recommended for patients with either a resting $PO_2$ of 55 mm Hg or a resting $PO_2$ of less than 60 mm Hg and evidence of cor pulmonale or polycythemia.

**References:** See page 255.

# *Infectious Diseases*

## Influenza

Influenza is an acute respiratory illness caused by influenza A or B viruses, which occurs in outbreaks and epidemics worldwide, mainly in the winter season. Signs and symptoms of upper and/or lower respiratory tract involvement are present, along with fever, headache, myalgia, and weakness. About 30% of the population is considered to be at high risk for serious complications of influenza. Each year, the virus infects 17 million to 50 million Americans.

## I. Pathophysiology

**A. Influenza A** is the predominant virus type, accounting for 99.5% of influenza cases. The incidence of influenza peaks in the last week of December. The optimal time to vaccinate is during October and November.

**B.** Oseltamivir (Tamiflu) and zanamivir (Relenza) block the neuraminidase surface protein on both influenza A and influenza B. Amantadine and rimantadine prevent early viral replication of influenza A only.

**Comparison of the anti-influenza drugs**

| Characteristic | Amantadine (Symmetrel) | Rimantadine (Flumadine) | Zanamivir (Relenza) | Oseltamivir (Tamiflu) |
|---|---|---|---|---|
| Chemical classification | Adamantamines | | Neuraminidase inhibitor | |
| Spectrum | Influenza A only | Influenza A only | Influenza A and B | Influenza A and B |
| Side effects | CNS (5%-30%): drowsiness, confusion, seizures, gastrointestinal upset | CNS: <6% Gastrointestinal upset | Bronchospasm in patients with reactive airway disease | Nausea and vomiting (8%-10%) |
| Approved indications | Treatment and prophylaxis of adults and children >1 yr | Treatment and prophylaxis of adults Treatment of children >14 yr and prophylaxis >1 yr | Treatment of adults and children >7 yr | Treatment of adults >18 yr Prophylaxis of adults and children >13 yr |
| Treatment dose | 200 mg/d or 100 mg PO bid | | 10 mg inhaled powder bid | 75 mg PO bid |
| Prophylaxis dose | Adults: 200 mg/d or 100 mg bid | | 10 mg inhaled powder qd | 75 mg qd |
| Length of therapy | 5-7 or 1-2 days after symptoms resolve | | 5 days | 5 days |
| Length of prophylaxis | 10 days | 10 days | Undetermined | 7 days post-exposure, 42 days seasonal outbreak |

## II. Clinical evaluation

**A.** Influenza begins with the abrupt onset of fever, headache, myalgia and malaise, accompanied by cough and sore throat. However, influenza infections also can present similar to the common cold or relatively little clinical indication of respiratory tract involvement.

**B. Physical examination.** The patient may appear hot and flushed; oropharyngeal abnormalities other than hyperemia are uncommon, even with complaints of severe sore throat. Mild cervical lymphadenopathy may be present.

**C. Complications of influenza.** Pneumonia is the most common complication of influenza, but central nervous system involvement may also occur.

## III. Diagnosis

**A.** Influenza is a disease that occurs in outbreaks or epidemics; in that setting, acute febrile respiratory illnesses can be diagnosed as influenza with a high degree of certainty by clinical criteria.

**B. Laboratory diagnosis** is accomplished by the detection of virus or viral antigen in throat swabs, nasal washes, or sputum. The most widely used technique is isolation of the virus in tissue culture, which can usually be accomplished within 48 to 72 hours of inoculation. Rapid viral diagnostic tests employing immunological techniques are becoming increasingly available, although they are less sensitive than conventional tissue culture.

**C.** For patients presenting during an epidemic with a typical influenza-like illness within 48 hours of symptom onset, a rapid diagnostic test such as direct fluorescent antigen should be performed. Therapy with an anti-influenza drug may be started before the test result is available.

**D.** If surveillance data indicate that influenza B is the predominant circulating virus, oseltamivir (Tamiflu) or zanamivir (Relenza) should be initiated. Adamantamines are appropriate for cases of suspected influenza A

## IV. Prevention and treatment of influenza

### A. Influenza vaccination

**1. Target groups for immunization.** The United States Public Health Service recommends influenza vaccine for groups at risk for influenza-related complications, including:

**a.** Persons 50 years of age or older

**b.**Residents of nursing homes and chronic care facilities that house persons with chronic medical conditions

**c.**Adults and children who have chronic disorders of the pulmonary or cardiovascular systems, including children with asthma

**d.**Adults and children who have required regular medical follow-up or hospitalization during the previous year because of chronic metabolic diseases including, diabetes mellitus, renal dysfunction, hemoglobinopathies, or immunosuppression (including immunosuppression secondary to medications or HIV)

**e.**Children and teenagers age 6 months to 18 years who are receiving long-term aspirin therapy

**f.**Women who will be in the second or third trimester of pregnancy during the influenza season

**2.**In addition, vaccination is recommended for individuals who might transmit influenza to persons at high risk, such as health-care workers, workers at chronic health-care facilities, providers of home care to persons at high risk, and household members of persons in high-risk groups.

**3.**The Advisory Committee on Immunization Practices (ACIP) of the CDC also recommends vaccination for household contacts and caretakers outside of the home of children between the ages of 0 to 23 months since young children are more likely to be hospitalized with influenza. This is especially important for contacts of those 0 to 5 months of age for whom influenza vaccine has not been approved. The ACIP also encourages vaccination for children between the ages of 6 to 23 months.

**4.**The ACIP recommends focusing on vaccinating the following groups in October: adults greater than or equal to 50 years of age, children 6 to 23 months of age, individuals 2 to 49 years with illnesses placing them at high risk, health-care workers, and household contacts of persons at high risk. Vaccination of others should be delayed until November.

**5.**The influenza vaccines are inactivated preparations of either whole virus or subvirion components. The intranasal influenza vaccine (FluMist) is approved for use in children over the age of five years and adults under the age of 50 years.

**6.Antiviral agents.** Antiviral drugs are also effective in the prevention and treatment of influenza. However, these agents should not be substituted for vaccination.

**7.Amantadine and rimantadine.** Amantadine and rimantadine are approved drugs for the prevention of influenza. They are active only against influenza A viruses and are 70 to 100 percent effective in the prophylaxis of influenza caused by these viruses.

**B.Prophylaxis.** For prophylaxis, amantadine or rimantadine need to be administered daily throughout the period of highest risk for influenza infection. These drugs may be particularly useful for individuals who have not been immunized, and can be administered simultaneously with an inactivated vaccine to provide protection until an immune response develops. Amantadine and rimantadine have also been used to control institutional outbreaks of influenza A.

**C.Treatment**

**1.Amantadine and rimantadine** have been effective in the treatment of influenza A. When administered within 48 hours of the onset of illness, amantadine or rimantadine reduces the duration of signs and symptoms of illness by 50 percent.

**a.**For adults, the recommended dose of amantadine or rimantadine for therapy of influenza is 200 mg per day for three to seven days. Amantadine and rimantadine are excreted via the kidney, and doses should be reduced to 100 mg per day or less in elderly patients and those with renal insufficiency.

**b.Side effects.** Amantadine is associated with jitteriness, insomnia, anxiety, and difficulty in concentration. Rimantadine appears to be as effective as amantadine and is associated with less frequent CNS side effects.

**2.Neuraminidase inhibitors**

**a.**Neuraminidase inhibitors are agents with in vitro activity against both influenza A and B viruses. Zanamivir (Relenza), an inhaled compound, and oseltamivir (Tamiflu), an orally ingested compound, are effective in the prophylaxis and therapy of influenza A and B infections. Zanamivir (Relenza) has been approved for the treatment of influenza for patients greater than or equal to 7 years of age and oseltamivir for patients greater than or equal to 18 years of age. Oseltamivir, but not zanamivir, has been approved for the prophylaxis of influenza in patients 13 years of age and older.

**b.Prevention.** The major benefit of neuraminidase inhibitors compared to amantadine and rimantadine is activity against influenza B. Both drugs have shown similar efficacy in preventing influenza as amantadine or rimantadine. Only oseltamivir (75 mg PO once or twice daily) has been approved for this use. Oseltamivir must be administered daily during the period of influenza activity.

**c.Treatment.** Both zanamivir (Relenza) and oseltamivir (Tamiflu) have been approved for the treatment of influenza in adults. Zanamivir is usually administered at an inhaled dose of 10 mg twice daily and oseltamivir (Tamiflu) 75 or 150 mg orally twice daily; the duration of therapy is five days. Each neuraminidase inhibitor decreases the duration and severity of influenza by approximately one day. These results are comparable to the benefits seen with amantadine and rimantadine.

**References:** See page 255.

# Pneumonia

Community-acquired pneumonia is the leading infectious cause of death and is the sixth-leading cause of death overall.

**I.Clinical diagnosis**

**A.Symptoms** of pneumonia may include fever, chills, malaise and cough. Patients also may have pleurisy, dyspnea, or hemoptysis. Eighty percent of patients are febrile.

**B.Physical exam findings** may include tachypnea, tachycardia, rales, rhonchi, bronchial breath sounds, and dullness to percussion over the involved area of lung.

**C.Chest radiograph** usually shows infiltrates. The chest radiograph may reveal multilobar infiltrates, volume loss, or pleural effusion. The chest radiograph may be negative very early in the illness because of dehydration or severe neutropenia.

**D.Additional testing** may include a complete blood count, pulse oximetry or arterial blood gas analysis.

**II.Laboratory evaluation**

**A.Sputum for Gram stain and culture** should be obtained in hospitalized patients. In a patient who has had no prior antibiotic therapy, a high-quality specimen (>25 white blood cells and <5 epithelial cells/hpf) may help to direct initial therapy.

**B.Blood cultures** are positive in 11% of cases, and cultures may identify a specific etiologic agent.

**C.Serologic testing for HIV** is recommended in hospitalized patients between the ages of 15 and 54 years. **Urine antigen testing** for legionella is indicated in endemic areas for patients with serious pneumonia.

**III.Indications for hospitalization**

**A.**Age >65years

**B.**Unstable vital signs (heart rate >140 beats per minute, systolic blood pressure <90 mm Hg, respiratory rate >30 beats per minute)

**C.**Altered mental status

**D.**Hypoxemia ($PO_2$ <60 mm Hg)

**E.**Severe underlying disease (lung disease, diabetes mellitus, liver disease, heart failure, renal failure)

**F.**Immune compromise (HIV infection, cancer, corticosteroid use)

**G.**Complicated pneumonia (extrapulmonary infection, meningitis, cavitation, multilobar involvement, sepsis, abscess, empyema, pleural effusion)

**H.**Severe electrolyte, hematologic or metabolic abnormality (ie, sodium <130 mEq/L, hematocrit <30%, absolute neutrophil count <1,000/$mm^3$, serum creatinine > 2.5 mg/dL)

**I.**Failure to respond to outpatient treatment within 48 to 72 hours.

**Pathogens Causing Community-Acquired Pneumonia**

| More Common | Less Common |
|---|---|
| Streptococcus pneumoniae<br>Haemophilus influenzae<br>Moraxella catarrhalis<br>Mycoplasma pneumoniae<br>Chlamydia pneumoniae<br>Legionella species<br>Viruses<br>Anaerobes (especially with aspiration) | Staphylococcus aureus<br>Gram-negative bacilli<br>Pneumocystis carinii<br>Mycobacterium tuberculosis |

**IV.Treatment of community-acquired pneumonia**

**Recommended Empiric Drug Therapy for Patients with Community-Acquired Pneumonia**

| Clinical Situation | Primary Treatment | Alternative(s) |
|---|---|---|
| Younger (<60 yr) outpatients without underlying disease | Macrolide antibiotics (azithromycin, clarithromycin, dirithromycin, or erythromycin) | Levofloxacin or doxycycline |
| Older (>60 yr) outpatients with underlying disease | Levofloxacin or cefuroxime or Trimethoprim-sulfamethoxazole<br>Add vancomycin in severe, life-threatening pneumonias | Beta-lactamase inhibitor (with macrolide if legionella infection suspected) |
| Gross aspiration suspected | Clindamycin IV | Cefotetan, ampicillin/sulbactam |

**A.Younger, otherwise healthy outpatients**

**1.**The most commonly identified organisms in this group are *S pneumoniae, M pneumoniae, C pneumoniae,* and respiratory viruses.

**2.**Erythromycin has excellent activity against most of the causal organisms in this group except *H influenzae.*

**3.**The newer macrolides, active against *H influenzae* (azithromycin [Zithromax] and clarithromycin [Biaxin]), are effective as empirical monotherapy for younger adults without underlying disease.

**B.Older outpatients with underlying disease**

**1.**The most common pathogens in this group are S *pneumoniae, H influenzae,* respiratory viruses, aerobic gram-negative bacilli, and S *aureus.* Agents such as *M pneumoniae* and C *pneumoniae* are not usually found in this group. *Pseudomonas aeruginosa* is rarely identified.

**2.**A second-generation cephalosporin (eg, cefuroxime [Ceftin]) is recommended for initial empirical treatment. Trimethoprim-sulfamethoxazole is an inexpensive alternative where pneumococcal resistance to not prevalent.

**3.**When legionella infection is suspected, initial therapy should include treatment with a macrolide antibiotic in addition to a beta-lactam/beta-lactamase inhibitor (amoxicillin clavulanate).

**C.Moderately ill, hospitalized patients**

**1.**In addition to S *pneumoniae* and *H influenzae,* more virulent pathogens, such as S *aureus, Legionella* species, aerobic gram-negative bacilli (including *P aeruginosa,* and anaerobes), should be considered in patients requiring hospitalization.

**2.**Hospitalized patients should receive an intravenous cephalosporin active against *S pneumoniae* and anaerobes (eg, cefuroxime, ceftriaxone [Rocephin], cefotaxime [Claforan]), or a beta-lactam/beta-lactamase inhibitor.

**3.Nosocomial pneumonia** should be suspected in patients with recent hospitalization or nursing home status. Nosocomial pneumonia is most commonly caused by Pseudomonas or Staph aureus. Empiric therapy should consist of vancomycin and double pseudomonal coverage with a beta-lactam (cefepime, Zosyn, imipenem, ticarcillin, ceftazidime, cefoperazone) and an aminoglycoside (amikacin, gentamicin, tobramycin) or a quinolone (ciprofloxacin).

**4.**When legionella is suspected (in endemic areas, cardiopulmonary disease, immune compromise), a macrolide should be added to the regimen. If legionella pneumonia is confirmed, rifampin (Rifadin) should be added to the macrolide.

**Common Antimicrobial Agents for Community-Acquired Pneumonia in Adults**

| Type | Agent | Dosage |
|---|---|---|
| **Oral therapy** | | |
| Macrolides | Erythromycin<br>Clarithromycin (Biaxin)<br>Azithromycin (Zithromax) | 500 mg PO qid<br>500 mg PO bid<br>500 mg PO on day 1, then 250 mg qd x 4 days |
| Beta-lactam/beta-lactamase inhibitor | Amoxicillin-clavulanate (Augmentin)<br>Augmentin XR | 500 mg tid or 875 mg PO bid<br>2 tabs q12h |
| Quinolones | Ciprofloxacin (Cipro)<br>Levofloxacin (Levaquin)<br>Ofloxacin (Floxin) | 500 mg PO bid<br>500 mg PO qd<br>400 mg PO bid |
| Tetracycline | Doxycycline | 100 m g PO bid |
| Sulfonamide | Trimethoprim-sulfamethoxazole | 160 mg/800 mg (DS) PO bid |
| **Intravenous Therapy** | | |
| Cephalosporins<br>Second-generation<br>Third-generation (anti-Pseudomonas aeruginosa) | Cefuroxime (Kefurox, Zinacef)<br>Ceftizoxime (Cefizox)<br>Ceftazidime (Fortaz)<br>Cefoperazone (Cefobid) | 0.75-1.5 g IV q8h<br>1-2 g IV q8h<br>1-2 g IV q8h<br>1-2 g IV q8h |
| Beta-lactam/beta-lactamase inhibitors | Ampicillin-sulbactam (Unasyn)<br>Piperacillin/tazobactam (Zosyn)<br>Ticarcillin-clavulanate (Timentin) | 1.5 g IV q6h<br>3.375 g IV q6h<br>3.1 g IV q6h |
| Quinolones | Ciprofloxacin (Cipro)<br>Levofloxacin (Levaquin)<br>Ofloxacin (Floxin) | 400 mg IV q12h<br>500 mg IV q24h<br>400 mg IV q12h |
| Aminoglycosides | Gentamicin<br>Amikacin | Load 2.0 mg/kg IV, then 1.5 mg/kg q8h |
| Vancomycin | Vancomycin | 1 gm IV q12h |

**D.Critically ill patients**

**1.**S *pneumoniae* and *Legionella* species are the most commonly isolated pathogens, and aerobic gram-negative bacilli are identified with increasing frequency. M pneumoniae, respiratory viruses, and H *influenzae* are less commonly identified.

**2.**Erythromycin should be used along with an antipseudomonal agent (ceftazidime, imipenem-cilastatin [Primaxin], or ciprofloxacin [Cipro]). An aminoglycoside should be added for additional antipseudomonal activity until culture results are known.

**3.**Severe life-threatening community-acquired pneumonias should be treated with vancomycin empirically until culture results are known. Twenty-five percent of S. pneumoniae isolates are no longer susceptible to penicillin, and 9% are no longer susceptible to extended-spectrum cephalosporins.

**4.**Pneumonia caused by penicillin-resistant strains of S. pneumoniae should be treated with high-dose penicillin G (2-3 MU IV q4h), or cefotaxime (2 gm IV q8h), or ceftriaxone (2 gm IV q12h), or meropenem (Merrem) (500-1000 mg IV q8h), or vancomycin (Vancocin) (1 gm IV q12h).

**5.**H. influenzae and Moraxella catarrhalis often produce beta-lactamase enzymes, making these organisms resistant to penicillin and ampicillin. Infection with these pathogens is treated with a second-generation cephalosporin, beta-lactam/beta-lactamase inhibitor combination such as amoxicillin-clavulanate, azithromycin, or trimethoprim-sulfamethoxazole.

**6.**Most bacterial infections can be adequately treated with 10-14 days of antibiotic therapy. A shorter treatment course of 3-5 days is possible with azithromycin because of its long half-life. M *pneumoniae and C pneumoniae* infections require treatment for up to 14 days. Legionella infections should be treated for a minimum of 14 days; immunocompromised patients require 21 days of therapy.

**References:** See page 255.

# Sinusitis

Sinusitis affects 12% of adults and complicates 0.5% of viral upper respiratory infections. Symptoms that have been present for less than 1 month are indicative of acute sinusitis, while symptoms of longer duration reflect chronic sinusitis.

**I.Pathophysiology**

**A.**Factors that predispose to sinus infection include anatomic abnormalities, viral URIs, allergies, overuse of topical decongestants, asthma, and immune deficiencies.

**B.Acute sinusitis** is associated with the same bacteria as otitis media. Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis are the most commonly encountered pathogens. Thirty-five percent of H influenzae and 75% of M catarrhalis strains produce beta-lactamases, making them resistant to penicillin antibiotics.

**C.Chronic sinusitis** is associated with Staphylococcus aureus and anaerobes.

**II.Clinical evaluation**

**A.**Symptoms of acute sinusitis include facial pain or tenderness, nasal congestion, purulent nasal and postnasal discharge, headache, maxillary tooth pain, malodorous breath, fever, and eye swelling. Pain or pressure in the cheeks and deep nasal recesses is common.

**B.**If symptoms have lasted for less than 7 to 10 days and the patient is recovering, a self-limited viral URI is the most likely cause. However, worsening symptoms or symptoms that persist for more than 7 days are more likely to be caused by sinusitis.

**C.**High fever and signs of acute toxicity are unusual except in the most severe cases. Purulent drainage in the patient's nose or throat may sometimes be seen.

**D.**The nasal mucosa is often erythematous and swollen. The presence of mucopus in the external nares or posterior pharynx is highly suggestive of sinusitis. Facial tenderness, elicited by percussion, is an unreliable sign of sinusitis.

**III.Laboratory evaluation**

**A.Imaging.** Plain films are usually unnecessary for evaluating acute sinusitis because of the high cost and relative insensitivity.

**B.CT scanning** is useful if the diagnosis remains uncertain or if orbital or intracranial complications are suspected. CT scanning is nonspecific and may demonstrate sinus abnormalities in 87% of patients with colds.

**C.MRI** is useful when fungal infections or tumors are a possibility.

**D.Sinus aspiration** is an invasive procedure, and is only indicated for complicated sinusitis, immunocompromise, failure to respond to multiple courses of empiric antibiotic therapy, or severe symptoms.

**E.**Cultures of nasal secretions correlate poorly with results of sinus aspiration.

**IV.Management of sinusitis**

**A.Antibiotic therapy for sinusitis**

**1.First-line agents**

**a.**Amoxicillin (Amoxil): Adults, 500 mg tid PO for 14 days. Children, 40 mg/kg/d in 3 divided doses.

**b.**Trimethoprim/sulfamethoxazole (Bactrim, Septra): Adults, 1 DS tab (160/800 mg) bid. Children, 8/40 mg/kg/d bid.

**c.**Erythromycin/sulfisoxazole (Pediazole): Children, 50/150 mg/kg/d qid.

**2.**A 10- to 14-day course of therapy is recommended; however, if the patient is improved but still symptomatic at the end of the course, the medication should be continued for an additional 5 to 7 days after symptoms subside.

**3.Broader-spectrum agents**

**a.**If the initial response to antibiotics is unsatisfactory, beta-lactamase-producing bacteria are likely to be present, and broad-spectrum therapy is required.

**b.**Amoxicillin/clavulanate (Augmentin): adults, 250 mg tid or 875 mg bid; children, 40 mg/kg/d in 3 divided doses.
**c.**Amoxicillin/clavulanate extended-release (Augmentin XR), 1000 mg tabs; 2 tabs q12h
**d.**Azithromycin (Zithromax): 500 mg as a single dose on day 1, then 250 mg qd.
**e.**Clarithromycin (Biaxin): 500 mg bid.
**f.**Cefuroxime axetil (Ceftin): adults, 250 mg bid; children, 125 mg bid.
**g.**Cefixime (Suprax): adults, 200 mg bid; children, 8 mg/kg/d bid.
**h.**Cefpodoxime (Vantin) 200 mg bid
**i.**Cefprozil (Cefzil) 250-500 mg qd-bid
**j.**Loracarbef (Lorabid) 400 mg bid.
**k.**Levofloxacin (Levaquin) 500 mg qd.

**4.Penicillin-resistant S. Pneumoniae** result from bacterial alterations in penicillin-binding proteins. Highly resistant strains are resistant to penicillin, trimethoprim/sulfamethoxazole (TMP/SMX), and third-generation cephalosporins. The prevalence of multiple-drug resistant S. pneumoniae is 20-35%. High dose amoxicillin (80 mg/kg/d), or amoxicillin plus amoxicillin/clavulanate, or clindamycin are options.

**B.Chronic sinusitis** is commonly caused by anaerobic organisms. 3-4 weeks of therapy or longer is required.

**C.Ancillary treatments**

**1.Steam and saline** improves drainage of mucus. Spray saline (NaSal) or a bulb syringe with a saline solution (1 tsp of salt in 1 quart of warm water) may be used.

**2.Decongestants**

**a.**Topical or systemic decongestants may be used in acute or chronic sinusitis. Phenylephrine (Neo-Synephrine) or oxymetazoline (Afrin) nasal drops or sprays are commonly used.
**b.**Oral decongestants, such as phenylephrine or pseudoephedrine, are active in areas not reached by topical agents.

**References:** See page 255.

## Tonsillopharyngitis

In about a quarter of patients with a sore throat, the disorder is caused by group A beta-hemolytic streptococcus. Treatment of streptococcal tonsillopharyngitis reduces the occurrence of subsequent rheumatic fever, an inflammatory disease that affects the joints and heart, skin, central nervous system, and subcutaneous tissues.

**I.Prevalence of pharyngitis**

**A.**Group A beta-hemolytic streptococcus (GABHS) typically occurs in patients 5-11 years of age, and it is uncommon in children under 3 years old. Most cases of GABHS occur in late winter and early spring.

**B.Etiologic causes of sore throat**

**1.Viral.** Rhinoviruses, influenza, Epstein-Barr virus

**2.Bacterial.** GABHS (Streptococcus pyogenes), Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus, anaerobes, Mycoplasma pneumoniae, Candida albicans.

**C.**In patients who present with pharyngitis, the major goal is to detect GABHS infection because rheumatic fever may result. Severe GABHS infections may also cause a toxic-shock-like illness (toxic strep syndrome), bacteremia, streptococcal deep tissue infections (necrotizing fascitis), and streptococcal cellulitis.

**II.Clinical evaluation of sore throat**

**A.**GABHS infection is characterized by sudden onset of sore throat, fever and tender swollen anterior cervical lymph nodes, typically in a child 5-11 years of age. Headache, nausea and vomiting may occur.

**B.**Cough, rhinorrhea and hoarseness are generally absent.

**III.Physical examination**

**A.**Streptococcal infection is suggested by erythema and swelling of the pharynx, enlarged and erythematous tonsils, tonsillar exudate, or palatal petechiae. The clinical diagnosis of GABHS infection is correct in only 50-75% of cases when based on clinical criteria alone.

**B.**Unilateral inflammation and swelling of the pharynx suggests peritonsillar abscess. Distortion of the posterior pharyngeal wall suggests a retropharyngeal abscess. Corynebacterium diphtheriae is indicated by a dull membrane which bleeds on manipulation. Viral infections may cause oral vesicular eruptions.

**C.**The tympanic membranes should be examined for erythema or a middle ear effusion.

**D.**The lungs should be auscultated because viral infection occasionally causes pneumonia.

**IV.Diagnostic testing**

**A.**Rapid streptococcal testing has a specificity of 90% and a sensitivity of 80%. A dry swab should be used to sample both the posterior wall and the tonsillar fossae, especially erythematous or exudative areas.

**B.Throat culture** is the most accurate test available for the diagnosis of GABHS pharyngitis.

**C.Diagnostic approach**

**1.**Patients presenting with an acute episode of pharyngitis should receive a rapid streptococcal antigen test. If the rapid test is negative, a culture should be done.

**2.**If the rapid test is positive, treatment with an antibiotic should be initiated for 10 days. The presence of physical and historical findings suggesting GABHS infection may also prompt the initiation of antibiotic therapy despite a negative rapid strep test.

**3.**After throat culture, presumptive therapy should be initiated. If the culture is positive for GABHS, a 10-day

course of therapy should be completed. If the culture is negative, antibiotics may be discontinued.

**V. Antibiotic therapy**

**A.** Starting antibiotic therapy within the first 24-48 hours of illness decreases the duration of sore throat, fever and adenopathy by 12-24 hours. Treatment also minimizes risk of transmission and of rheumatic fever.

**B. Penicillin VK** is the antibiotic of choice for GABHS; 250 mg PO qid or 500 mg PO bid x 10 days [250, 500 mg]. A 10-day regimen is recommended. Penicillin G benzathine (Bicillin LA) may be used as one-time therapy when compliance is a concern; 1.2 million units IM x 1 dose.

**C. Azithromycin (Zithromax)** offers the advantage of once-a-day dosing for just 5 days; 500 mg x 1, then 250 mg qd x 4 days [6 pack].

**D. Clarithromycin (Biaxin)**, 500 mg PO bid; bacteriologic efficacy is similar to that of penicillin VK, and it may be taken twice a day.

**E. Erythromycin** is also effective; 250 mg PO qid; or enteric coated delayed release tablet (PCE) 333 mg PO tid or 500 mg PO bid [250, 333, 500 mg]. **Erythromycin ethyl succinate (EES)** 400 PO qid or 800 mg PO bid [400 mg]. Gastrointestinal upset is common.

**VI. Treatment of recurrent GABHS pharyngitis**

**A.** When patient compliance is an issue, an injection of penicillin G benzathine may be appropriate. When patient compliance is not an issue, therapy should be changed to a broader spectrum agent.

1. **Cephalexin (Keflex)** 250-500 mg tid x 5 days [250, 500 mg]
2. **Cefadroxil (Duricef)** 500 mg bid x 5 days [500 mg]
3. **Loracarbef (Lorabid)** 200-400 mg bid x 5 days [200, 400 mg]
4. **Cefixime (Suprax)** 400 mg qd x 5 days [200, 400 mg]
5. **Ceftibuten (Cedax)** 400 mg qd x 5 days [400 mg]
6. **Cefuroxime axetil (Ceftin)** 250-500 mg bid x 5 days [125, 250, 500 mg]

**B. Amoxicillin/clavulanate (Augmentin)** has demonstrated superior results in comparison with penicillin; 250-500 mg tid or 875 mg bid [250, 500, 875 mg].

**C.** Sulfonamides, trimethoprim, and the tetracyclines are not effective for the treatment of GABHS pharyngitis.

**References:** See page 255.

# Primary Care of the HIV-Infected Adult

**I. Initial evaluation**

**A.** The initial evaluation of the HIV-infected adult should include an assessment of the patient's past medical history, current symptoms and treatments, a complete physical examination, and laboratory testing.

**B. Previous conditions**

1. Prior medical conditions related to HIV infection should be assessed. Mucocutaneous candidiasis, oral hairy leukoplakia, hepatitis, pneumonia, sexually transmitted diseases, and tuberculosis should be sought. Past episodes of varicella-zoster, herpes simplex virus lesions, and opportunistic infections should be assessed.
2. Dates and results of earlier tuberculin skin tests should be obtained. Women should be are asked about dates and results of Pap smears. Previous immunizations and antiretroviral therapy should be documented.

**C. Current conditions and symptoms.** Fever, night sweats, unexplained weight loss, lymphadenopathy, oral discomfort, visual changes, unusual headaches, swallowing difficulties, diarrhea, dermatologic conditions, and respiratory and neurologic symptoms are suggestive of opportunistic infections or a malignant process.

**D. Social history** includes information on past and present drug use, sexual behavior, dietary habits, household pets, employment, and current living situation. Residence and travel history should be assessed because coccidioidomycosis and histoplasmosis are more common in certain geographic regions.

**II. Physical examination**

**A.** Weight, temperature, skin, oropharynx, fundi, lymph nodes, lungs, abdominal organs, genitalia, rectum, and the nervous system should be assessed. A cervical Pap smear should be obtained from women who have not had a normal result in the past year.

**B.** Screening for Neisseria gonorrhoeae and chlamydial infection should be considered for sexually active men and women.

**III. Laboratory tests**

**A. Complete blood count, chemistry profile, and serologic studies** for syphilis (rapid plasma reagin or VDRL), Toxoplasma gondii (IgG antibody), and hepatitis B (surface antigen, core antibody) should be obtained.

**B.** Patients should have a tuberculin skin test unless they have been reactive in the past or have been treated for the disease. In HIV-infected persons, a positive test is 5 mm or more of induration.

**C. A baseline chest film** is useful because many opportunistic pulmonary infections present with very subtle radiographic findings. A chest radiograph may suggest unrecognized tuberculosis.

**D. $CD4^+$ counts** assist in determination of the degree of immunologic damage, assess risk of opportunistic complications, and guide the use of prophylaxis against infections.

**E. HIV RNA levels**

1. Quantitation of plasma HIV RNA (viral load), a marker of the rate of viral replication, is useful in determining prognosis. It is used to estimate the risk of disease progression and to aid in making antiretroviral therapy decisions.
2. HIV RNA levels generally vary no more than 0.3 log in clinically stable patients. Sustained changes greater

than threefold (0.5 log) are significant. A decrease occurs with successful antiretroviral therapy. Increases noted during treatment suggest antiretroviral drug failure or poor adherence.

| Treatment Goals for HIV RNA Levels | |
|---|---|
| **Parameter** | **Recommendation** |
| Target level of HIV RNA after initiation of treatment | Undetectable; <below 50 copies of HIV RNA per mL |
| Minimal decrease in HIV RNA indicative of antiretroviral activity | >0.5 $\log_{10}$ decrease |
| Change in HIV RNA that suggests drug treatment failure | Rise in HIV RNA level<br>Failure to achieve desired reduction in HIV RNA level |
| Suggested frequency of HIV RNA measurement | At baseline: 2 measurements, 2-4 wk apart.<br>3-4 wk after initiating or changing therapy<br>Every 3-4 mo in conjunction with $CD4^+$ counts |

**3.**HIV RNA levels should be obtained before the initiation or change of antiretroviral therapy. The next determination should be done a month after therapeutic intervention to assess its effect and then every 3 or 4 months.

**4.**Quantitative HIV RNA assays include branched DNA (bDNA) (Multiplex) and reverse transcriptase-initiated polymerase chain reaction (RT-PCR) (Amplicor HIV-1 Monitor). While both tests provide similar information, concentrations of HIV RNA obtained with the RT-PCR test are about twofold higher than those obtained by the bDNA method. For this reason, all HIV RNA determinations in a single patient should be obtained using the same assay.

## IV.Antiretroviral therapy

**A.**Antiretroviral drug regimens may suppress HIV replication almost completely in some patients. These changes are associated with improved survival and a lengthening in the time to development of AIDS-defining conditions.

| Antiretroviral Therapy |
|---|
| **Initiate therapy for patients with:**<br>Symptomatic HIV disease<br>Asymptomatic HIV disease but $CD4^+$ count <350 cells/μL<br>HIV RNA levels >30,000 (bDNA) or >55,000 (RT-PCR) |
| **Consider therapy for patients with:**<br>Detectable HIV RNA levels who request it and are committed to lifelong adherence |
| **Change therapy for:**<br>Treatment failure, as indicated by<br>Rising HIV RNA level<br>Failure to achieve target decrease in HIV RNA<br>Declining $CD4^+$ count<br>Clinical progression<br>Toxicity, intolerance, or nonadherance |

| Recommended Antiretroviral Agents for Initial Treatment of Established HIV Infection | |
|---|---|
| Antiretroviral drug regimens are comprised of one choice each from columns A and B. Drugs are listed in alphabetical order. | |
| **Column A** | **Column B** |
| Efavirenz (Sustiva)<br>Indinavir (Crixivan)<br>Nelfinavir (Viracept)<br>Ritonavir (Norvir) + Indinavir (Kaletra)<br>Ritonavir + Lopinavir<br>Ritonavir + Saquinavir (Fortovase or Invirase) | Didanosine (Videx) + Lamivudine (Epivir)<br>Stavudine (Zerit) + Didanosine<br>Stavudine + Lamivudine<br>Zidovudine (Retrovir) + Didanosine<br>Zidovudine + Lamivudine |

## V.Prevention of infections

### A.Vaccinations

**1.**Vaccination with pneumococcal vaccine, polyvalent (Pneumovax 23, Pnu-Immune 23) is recommended when HIV infection is diagnosed. Yearly influenza vaccination is suggested. Those who are seronegative for hepatitis B and at risk for infection should be offered hepatitis B vaccine (Recombivax HB, Engerix-B).

**2.**Tetanus vaccine should be administered every 10 years, and hepatitis A vaccine (Havrix, Vaqta) should be considered for nonimmune sexually active patients.

### B.Opportunistic infections

**1.Pneumocystis carinii pneumonia** is rarely encountered in patients receiving prophylactic therapy. Indications for prophylaxis are a $CD4^+$ count below 200 cells/μL, HIV-related thrush, or unexplained fever for 2 or more weeks regardless of $CD4^+$ count. Anyone with a past history of PCP should continue suppressive therapy indefinitely because of the high risk of relapse.

**2.Toxoplasmosis** risk increases as the $CD4^+$ count approaches 100 cells/μL, and patients who are seropositive for IgG antibody to toxoplasma should begin preventive therapy when the count nears this level. Patients who have been treated for toxoplasmosis require lifelong suppressive therapy.

**USPHS/IDSA Guidelines for Prevention of Opportunistic Infections in HIV-Infected Patients**

| Pathogen | Indication for prophylaxis | First-choice drug | Selected alternative drugs |
|---|---|---|---|
| **Prophylaxis Strongly Recommended** | | | |
| Pneumocystis carinii | $CD4^+$ count <200 cells/µL or unexplained fever for >2 wk or oropharyngeal candidiasis | TMP-SMX (Bactrim, Septra), 1 DS tablet PO daily | Dapsone, 100 mg PO daily, or aerosolized pentamidine (NebuPent), 300 mg monthly |
| Mycobacterium tuberculosis | Tuberculin skin test reaction of >5 mm or prior positive test without treatment or exposure to active tuberculosis | Isoniazid, 300 mg PO, plus pyridoxine, 50 mg PO daily for 12 mo | Rifampin, 600 mg PO daily for 12 mo |
| Toxoplasma gondii | IgG antibody to T gondii and $CD4^+$ count <100 cells/µL | TMP-SMX, 1 DS tablet PO daily | Dapsone, 50 mg PO daily, plus pyrimethamine (Daraprim), 50 mg PO weekly, plus leucovorin (Wellcovorin), 25 mg PO weekly |
| Mycobacterium avium complex | $CD4^+$ <50 cells/µL | Clarithromycin (Biaxin), 500 mg PO bid, or azithromycin (Zithromax), 1,200 mg PO weekly | Rifabutin (Mycobutin), 300 mg PO daily |
| Streptococcus pneumoniae | All patients | Pneumococcal vaccine (Pneumovax 23, Pnu-Immune 23), 0.5 mL IM once | None |
| **Consideration of Prophylaxis Recommended** | | | |
| Hepatitis B virus | All seronegative patients | Hepatitis B vaccine (Engerix-B, 20 pg IM x 3, or Recombivax HB, 10 µg IM x 3) | None |
| Influenza virus | All patients, annually before influenza season | 0.5 mL IM | Rimantadine (Flumadine), 100 mg PO bid, or amantadine (Symadine, Symmetrel), 100 mg PO bid |

**C.Tuberculosis**. Patients who have HIV infection and positive results on tuberculin skin tests have a 2-10% per year risk of reactivation. If active tuberculosis has been excluded, prophylaxis should be prescribed to HIV-infected patients who have a tuberculin skin test reaction of 5 mm or more, who have a history of a positive tuberculin skin test reaction but were never treated, or who have had close contact with someone with active tuberculosis.
**D.Mycobacterium avium complex infection.** Prophylactic therapy is recommended for patients whose $CD4^+$ counts are less than 50 cells/µL. Azithromycin (Zithromax), 1,200 mg (2 tabs) weekly by mouth is recommended.

**References:** See page 255.

# Diverticulitis

By age 50, one-third of adults have diverticulosis coli; two-thirds have diverticulosis by age 80. Diverticulitis or diverticular hemorrhage occurs in 10-20% of patients with diverticulosis. Causes of diverticulosis include aging, elevation of colonic intraluminal pressure, and decreased dietary fiber. Eighty-five percent are found in the sigmoid colon.

**I.Clinical presentation of diverticulitis**
**A.**Diverticulitis is characterized by the abrupt onset of unremitting left-lower quadrant abdominal pain, fever, and an alteration in bowel pattern. Diverticulitis of the transverse colon may simulate ulcer pain; diverticulitis of the cecum and redundant sigmoid may resemble appendicitis.
**B.Physical exam.** Left-lower quadrant tenderness is characteristic. Abdominal examination is often deceptively unremarkable in the elderly and in persons taking corticosteroids.

| Differential Diagnosis of Diverticulitis | |
|---|---|
| **Elderly** | **Middle Aged and Young** |
| Ischemic colitis<br>Carcinoma<br>Volvulus<br>Colonic Obstruction<br>Penetrating ulcer<br>Nephrolithiasis/urosepsis | Appendicitis<br>Salpingitis<br>Inflammatory bowel disease<br>Penetrating ulcer<br>Urosepsis |

**II.Diagnostic evaluation**

**A.Plain X-rays** may show ileus, obstruction, mass effect, ischemia, or perforation.

**B.CT scan with contrast** is the test of choice to evaluate acute diverticulitis. The CT scan can be used for detecting complications and ruling out other diseases.

**C.Contrast enema.** Water soluble contrast is safe and useful in mild-to-moderate cases of diverticulitis when the diagnosis is in doubt.

**D.Endoscopy.** Acute diverticulitis is a relative contraindication to endoscopy; perforation should be excluded first. Endoscopy is indicated when the diagnosis is in doubt to exclude the possibility of ischemic bowel, Crohn's disease, or carcinoma.

**E.Complete blood count** may show leukocytosis.

**III.Treatment**

**A.Outpatient treatment**

**1.Clear liquid diet**

**2.Oral antibiotics**

**a.**Ciprofloxacin (Cipro) 500 mg PO bid **AND**

**b.**Metronidazole (Flagyl) 500 mg PO qid.

**B.Inpatient treatment**

**1.**Severe cases require hospitalization for gastrointestinal tract rest (NPO), intravenous fluid hydration, and antibiotics. Nasogastric suction is initiated if the patient is vomiting or if there is abdominal distention.

**2.**Antibiotic coverage should include enteric gram-negative and anaerobic organisms

**a.**Ampicillin 1-2 gm IV q4-6h **AND**

**b.**Gentamicin or tobramycin 100-120 mg IV (1.5-2 mg/kg), then 80 mg IV q8h (5 mg/kg/d) **AND**

**c.**Metronidazole (Flagyl) 500 mg IV q6-8h (15-30 mg/kg/d) **OR**

**d.**Cefoxitin (Mefoxin) 2 gm IV q6h **OR**

**e.**Piperacillin-tazobactam (Zosyn) 3.375-4.5 gm IV q6h.

**C.**Failure to improve or deterioration are indications for reevaluation and consideration of surgery. Analgesics should be avoided because they may mask acute deterioration, and they may obscure the need for urgent operation.

**D.**Oral antibiotics should be continued for 1-2 weeks after resolution of the acute attack. Ciprofloxacin, 500 mg PO bid.

**E.**After the acute attack has resolved, clear liquids should be initiated, followed by a low residue diet for 1-2 weeks, followed by a high-fiber diet with psyllium.

**IV.Surgical therapy**

**A.**An emergency sigmoid colectomy with proximal colostomy is indicated for attacks of diverticulitis associated with sepsis, peritonitis, obstruction, or perforation.

**B.**Elective sigmoid resection is indicated for second or subsequent attacks of diverticulitis, or for attacks with complications managed nonoperatively (eg, percutaneous CT-guided drainage of an abscess), or carcinoma.

**C.Operative procedures**

**1.Single-stage procedure.** This procedure is usually performed as an elective procedure after resolution of the acute attack of diverticulitis. The segment containing inflamed diverticulum (usually sigmoid colon) is resected with primary anastomosis. A bowel prep is required.

**2.Two-stage procedure.** This procedure is indicated for acute diverticulitis with obstruction or perforation with an unprepared bowel. The first stage consists of resection of the involved segment of colon with end colostomy and either a mucous fistula or a Hartmann rectal pouch. The second stage consists of a colostomy take-down and reanastomosis after 2-3 months.

**References:** See page 255.

# Urinary Tract Infection

Urinary tract infections (UTIs) are a leading cause of morbidity in persons of all ages. Sexually active young women, elderly persons and those undergoing genitourinary instrumentation or catheterization are at risk.

**I.Acute uncomplicated cystitis in young women**

**A.**Sexually active young women are most at risk for UTIs.

**B.**Approximately 90 percent of uncomplicated cystitis episodes are caused by Escherichia coli, 10 to 20 percent are caused by coagulase-negative Staphylococcus saprophyticus and 5 percent or less are caused by other Enterobacteriaceae organisms or enterococci. Up to one-third of uropathogens are resistant to ampicillin and, but the majority are susceptible to trimethoprim-sulfamethoxazole (85 to 95 percent) and fluoroquinolones (95 percent).

**C.**Patients should be evaluated for pyuria by urinalysis (wet mount examination of spun urine) or a dipstick test for leukocyte esterase.

| Urinary Tract Infections in Adults |
|---|

| Category | Diagnostic criteria | First-line therapy | Comments |
|---|---|---|---|
| Acute uncomplicated cystitis | Urinalysis for pyuria and hematuria (culture not required) | TMP-SMX DS (Bactrim, Septra)<br>Trimethoprim (Proloprim)<br>Ciprofloxacin (Cipro)<br>Ofloxacin (Floxin) | Three-day course is best<br>Quinolones may be used in areas of TMP-SMX resistance or in patients who cannot tolerate TMP-SMX |
| Recurrent cystitis in young women | Symptoms and a urine culture with a bacterial count of more than 100 CFU per mL of urine | If the patient has more than three cystitis episodes per year, treat prophylactically with postcoital, patient- directed or continuous daily therapy | Repeat therapy for seven to 10 days based on culture results and then use prophylactic therapy |
| Acute cystitis in young men | Urine culture with a bacterial count of 1,000 to 10,000 CFU per mL of urine | Same as for acute uncomplicated cystitis | Treat for seven to 10 days |
| Acute uncomplicated pyelonephritis | Urine culture with a bacterial count of 100,000 CFU per mL of urine | If gram-negative organism, oral fluoroquinolone<br>If gram-positive organism, amoxicillin<br>If parenteral administration is required, ceftriaxone (Rocephin) or a fluoroquinolone<br>If Enterococcus species, add oral or IV amoxicillin | Switch from IV to oral administration when the patient is able to take medication by mouth; complete a 14-day course |
| Complicated urinary tract infection | Urine culture with a bacterial count of more than 10,000 CFU per mL of urine | If gram-negative organism, oral fluoroquinolone<br>If Enterococcus species, ampicillin or amoxicillin with or without gentamicin (Garamycin) | Treat for 10 to 14 days |
| Catheter-associated urinary tract infection | Symptoms and a urine culture with a bacterial count of more than 100 CFU per mL of urine | If gram-negative organism, a fluoroquinolone<br>If gram-positive organism, ampicillin or amoxicillin plus gentamicin | Remove catheter if possible, and treat for seven to 10 days<br>For patients with long-term catheters and symptoms, treat for five to seven days |

**Antibiotic Therapy for Urinary Tract Infections**

| Diagnostic group | Duration of therapy | Empiric options |
|---|---|---|
| Acute uncomplicated urinary tract infections in women | Three days | Trimethoprim-sulfamethoxazole (Bactrim DS), one double-strength tablet PO twice daily<br>Trimethoprim (Proloprim), 100 mg PO twice daily<br>Norfloxacin (Noroxin), 400 mg twice daily<br>Ciprofloxacin (Cipro), 250 mg twice daily<br>Lomefloxacin (Maxaquin), 400 mg per day<br>Ofloxacin (Floxin), 200 mg twice daily<br>Enoxacin (Penetrex), 200 mg twice daily<br>Sparfloxacin (Zagam), 400 mg as initial dose, then 200 mg per day<br>Levofloxacin (Levaquin), 250 mg per day<br>Nitrofurantoin (Macrodantin), 100 mg four times daily<br>Cefpodoxime (Vantin), 100 mg twice daily<br>Cefixime (Suprax), 400 mg per day<br>Amoxicillin-clavulanate(Augmentin), 500 mg twice daily |
| Acute uncomplicated pyelonephritis | 14 days | Trimethoprim-sulfamethoxazole DS, one double-strength tablet PO twice daily<br>Ciprofloxacin (Cipro), 500 mg twice daily<br>Levofloxacin (Maxaquin), 250 mg per day<br>Enoxacin (Penetrex), 400 mg twice daily<br>Sparfloxacin (Zagam) 400 mg initial dose, then 200 mg per day 104.50<br>Ofloxacin (Floxin), 400 mg twice daily<br>Cefpodoxime (Vantin), 200 mg twice daily<br>Cefixime (Suprax), 400 mg per day |
| | Up to 3 days | Trimethoprim-sulfamethoxazole (Bactrim) 160/800 IV twice daily<br>Ceftriaxone (Rocephin), 1 g IV per day<br>Ciprofloxacin (Cipro), 400 mg twice daily<br>Ofloxacin (Floxin), 400 mg twice daily<br>Levofloxacin (Penetrex), 250 mg per day<br>Aztreonam (Azactam), 1 g three times daily<br>Gentamicin (Garamycin), 3 mg per kg per day in 3 divided doses every 8 hours |
| Complicated urinary tract infections | 14 days | Fluoroquinolones PO |
| | Up to 3 days | Ampicillin, 1 g IV every six hours, and gentamicin, 3 mg per kg per day |
| Urinary tract infections in young men | Seven days | Trimethoprim-sulfamethoxazole, one double-strength tablet PO twice daily<br>Fluoroquinolones |

**D.Treatment of acute uncomplicated cystitis in young women**

**1.**Three-day regimens appear to offer the optimal combination of convenience, low cost and an efficacy comparable to that of seven-day or longer regimens.

**2.**Trimethoprim-sulfamethoxazole is the most cost-effective treatment. Three-day regimens of ciprofloxacin (Cipro), 250 mg twice daily, and ofloxacin (Floxin), 200 mg twice daily, produce better cure rates with less toxicity.

**3.**Quinolones that are useful in treating complicated and uncomplicated cystitis include ciprofloxacin, norfloxacin, ofloxacin, enoxacin (Penetrex), lomefloxacin (Maxaquin), sparfloxacin (Zagam) and levofloxacin (Levaquin).

**4.**Trimethoprim-sulfamethoxazole remains the antibiotic of choice in the treatment of uncomplicated UTIs in young women. Fluoroquinolones are recommended for patients who cannot tolerate sulfonamides or trimethoprim or who have a high frequency of antibiotic resistance. Three days is the optimal duration of treatment for uncomplicated cystitis. A seven-day course should be considered in pregnant women, diabetic women and women who have had symptoms for more than one week.

**II.Recurrent cystitis in young women**

**A.**Up to 20 percent of young women with acute cystitis develop recurrent UTIs. The causative organism should be identified by urine culture.

**B.**Women who have more than three UTI recurrences within one year can be managed using one of three preventive strategies.

**1.**Acute self-treatment with a three-day course of standard therapy.

**2.**Postcoital prophylaxis with one-half of a trimethoprim-sulfamethoxazole double-strength tablet (40/200 mg).

**3.**Continuous daily prophylaxis for six months with trimethoprim-sulfamethoxazole, one-half tablet per day (40/200 mg); nitrofurantoin, 50 to 100 mg per day; norfloxacin (Noroxin), 200 mg per day; cephalexin (Keflex), 250 mg per day; or trimethoprim (Proloprim), 100 mg per day.

**III.Complicated UTI**

**A.**A complicated UTI is one that occurs because of enlargement of the prostate gland, blockages, or the presence of resistant bacteria.

**B.**Accurate urine culture and susceptibility are necessary. Treatment consists of an oral fluoroquinolone. In patients who require hospitalization, parenteral administration of ceftazidime (Fortaz) or cefoperazone (Cefobid), cefepime (Maxipime), aztreonam (Azactam), imipenem-cilastatin (Primaxin) or the combination of an antipseudomonal penicillin (ticarcillin [Ticar], mezlocillin [Mezlin], piperacillin [Pipracil]) with an aminoglycoside.

**C.**Enterococci are frequently encountered uropathogens in complicated UTIs. In areas in which vancomycin-resistant Enterococcus faecium is prevalent, quinupristin-dalfopristin (Synercid) may be useful.

**D.**Patients with complicated UTIs require at least a 10- to 14-day course of therapy. Follow-up urine cultures should be performed within 10 to 14 days after treatment.

**IV.Uncomplicated pyelonephritis**

**A.**Women with acute uncomplicated pyelonephritis may present with a mild cystitis-like illness and flank pain; fever, chills, nausea, vomiting, leukocytosis and abdominal pain; or a serious gram-negative bacteremia. Uncomplicated pyelonephritis is usually caused by E. coli.

**B.**The diagnosis should be confirmed by urinalysis and by urine culture. Urine cultures demonstrate more than 100,000 CFU per mL of urine in 80 percent of women with pyelonephritis. Blood cultures are positive in up to 20 percent of women who have this infection.

**C.**Empiric therapy using an oral fluoroquinolone is recommended in women with mild to moderate symptoms. Patients who are too ill to take oral antibiotics should initially be treated with a parenterally third-generation cephalosporin, aztreonam, a broad-spectrum penicillin, a quinolone or an aminoglycoside.

**D.**The total duration of therapy is usually 14 days. Patients with persistent symptoms after three days of antimicrobial therapy should be evaluated by renal ultrasonography for evidence of urinary obstruction or abscess.

**References:** See page 255.

## Herpes Simplex Virus Infections

Herpes simplex virus (HSV) affects more than one-third of the world's population. Ninety percent of infections caused by HSV-2 are genital, and 90 percent of those caused by HSV-1 are oral.

**I.Diagnosis**

**A.**The diagnosis of genital HSV infection may be made clinically, but laboratory confirmation is recommended in patients presenting with primary or suspected recurrent infection. The gold standard of diagnosis is viral isolation by tissue culture, although this process can take as long as four to five days, and the sensitivity rate is 70 to 80 percent.

**B.**Antigen detection tests have lower sensitivity rates (50 to 70 percent) than viral culture.

**II.Genital Herpes**

**A.**Genital HSV infection is usually transmitted through sexual contact. About 22 percent of adults have serologic evidence of HSV-2 infection.

**B.Clinical Presentation**

**1.**Primary genital herpes has an incubation period of two to 12 days, followed by a prodrome of itching, burning or erythema. Multiple transient, painful vesicles then appear on the penis, perineum, vulva, vagina or cervix, and tender inguinal lymphadenopathy may follow. The initial ulceration crusts and heals by 14 to 21 days. Fever, headache, malaise, abdominal pain and myalgia are common in primary disease. Recurrences are usually less severe and shorter in duration.

**2.**Women with established genital HSV-2 infection have asymptomatic shedding 1 to 5 percent of days.

**C.Treatment of Primary Infection**

**1.**Antiviral therapy is recommended for the initial genital herpes outbreak. Oral acyclovir is effective in reducing symptoms. Topical acyclovir reduces the length of time before all lesions become crusted but is much less effective than oral acyclovir.

**2.**The oral acyclovir dosage for treatment of primary or initial nonprimary genital herpes is 200 mg five times daily for 10 days.

**3.**Valacyclovir, given twice daily, is effective for the treatment of primary genital herpes but costs more than acyclovir. Famciclovir, given three times daily, is as effective as acyclovir, although it may be twice as expensive.

| Dosage Regimens for Primary Genital Herpes Infection | |
|---|---|
| **Drug** | **Dosage** |
| Acyclovir (Zovirax) | 200-400 mg three times daily for 10 days |
| Famciclovir (Famvir) | 250 mg three times daily for 10 days |
| Valacyclovir (Valtrex) | 1 g twice daily for 10 days |

**D.Treatment of Recurrent Infection**

**1.**Drug therapy to prevent recurrences is effective; it is prescribed for use in patients who have more than six outbreaks per year.

**2.**Acyclovir has been used to suppress recurrences of genital herpes, decreasing the frequency by 80 percent and preventing recurrence by 45 percent.

**3.**Famciclovir and valacyclovir are as effective as acyclovir in suppressing recurrent genital herpes. Valacyclovir has the advantage of once-daily dosing. Famciclovir must be given twice daily.

| Dosages and Characteristics of Chronic Suppressive Treatment Regimens for Recurrent Genital Herpes Infection | | | |
|---|---|---|---|
| **Drug** | **Dosage** | **Decrease in recurrence rate (percentage)** | **Use in patients with ≥6 recurrences per year** |
| Acyclovir (Zovirax) | 400 mg twice daily | 78 to 79 | Yes |
| Famciclovir (Famvir) | 250 mg twice daily | 79 | Yes |
| Valacyclovir (Valtrex) | 1 g once daily | 78 to 79 | Yes |
| | 250 mg twice daily | 78 to 79 | Yes |
| | 500 mg once daily | 71 | No |
| | 250 mg once daily | 54 | No |

**E.Episodic Therapy**. Acyclovir, taken hours after the prodrome of recurrence begins, exerts a benefit in recurrent genital herpes. Famciclovir and valacyclovir are slightly more effective than acyclovir for the treatment of recurrent infections.

| Dosages of Antiviral Agents for Treatment of Episodic Genital Herpes | |
|---|---|
| **Drug** | **Dosage** |
| Acyclovir (Zovirax) | 200 mg 5 times daily for 5 days<br>800 mg twice daily for 5 days |
| Famciclovir (Famvir) | 125 mg twice daily for 5 days |
| Valacyclovir (Valtrex) | 500 mg twice daily for 5 days |

**III.Orolabial Herpes**

**A.**Orolabial herpes (gingivostomatitis) is the most prevalent form of herpes infection; 35 to 60 percent of persons show serologic evidence of having been infected by HSV-1.

**B.**Primary herpetic gingivostomatitis usually affects children under the age of five. It appears as painful vesicles and ulcerative erosions on the tongue, palate, gingiva, buccal mucosa and lips.

**C.**Systemic symptoms are often present, including fever (38.4 to 40˚C), malaise and myalgia. The duration of the illness is two to three weeks, and oral shedding of virus may continue for a 23 days.

**D.**Recurrences typically occur two or three times a year. The duration is shorter and the discomfort less severe than in primary infections, and the vesicles heal completely by eight to 10 days.

**E.Treatment of Primary Infection**

**1.**Topical medication for HSV infection is not highly effective. Topical penciclovir, applied every two hours for four days, reduces healing time by only about one day.

**2.**Oral acyclovir, in a dosage of 200 mg five times daily for five days, accelerates loss of crusts by one day (seven versus eight days) and can reduce the duration of pain by 36 percent

**F.Treatment of Recurrent Infection**

**1.**Oral acyclovir, in dosages ranging from 400 to 1,000 mg daily, is effective in reducing by 50 to 78 percent the frequency of herpes labialis following UV light exposure. Oral acyclovir may lessen the severity of lesions. Short-term prophylactic therapy with acyclovir may be desirable in some patients who anticipate intense exposure to UV light (eg, skiers).

**2.**Early treatment of recurrent orolabial HSV infection with high dosages of antiviral medication markedly decreases the size and duration of lesions. Famciclovir, in a dosage of 250 mg three times daily for five days decreases lesion surface area by 50 percent and accelerates healing time.

**References:** See page 255.

# Herpes Zoster and Postherpetic Neuralgia

Herpes zoster (shingles) results from reactivation of the varicella-zoster virus. Herpes zoster has a lifetime incidence of 10 to 20 percent. The incidence of herpes zoster increases sharply with advancing age, doubling in each decade past the age of 50 years.

**I.Clinical evaluation**

**A.**Herpes zoster typically presents with a prodrome consisting of hyperesthesia, paresthesias, burning dysesthesias or pruritus along the affected dermatome(s). The prodrome generally lasts one to two days.

**B.**The prodromal phase is followed by development of a maculopapular rash that follows a dermatomal distribution. The maculopapular rash evolves into vesicles with an erythematous base. The vesicles are painful, and their development is often associated with flu-like symptoms.

**C.**Although any vertebral dermatome may be involved, T5 and T6 are most commonly affected. The most frequently involved cranial nerve dermatome is the ophthalmic division of the trigeminal nerve.

**D.**The most common chronic complication of herpes zoster is postherpetic neuralgia. Pain that persists for longer than one to three months after resolution of the rash is a sign of postherpetic neuralgia. Affected patients usually report constant burning, lancinating pain. Symptoms tend to abate over time. Less than one-quarter of patients still experience pain at six months after the herpes zoster eruption, and fewer than one in 20 has pain at one year.

**II.Treatment of herpes zoster**

**A.Acyclovir (Zovirax)**

**1.**Oral acyclovir ([ACV] 800 mg five times daily) has been the mainstay of herpes zoster treatment. Acyclovir is effective in accelerating acute pain resolution when started within 48 hours of the onset of the rash. A more marked benefit was noted in patients over the age of 50 years. The poor bioavailability of oral ACV requires an inconvenient schedule of five times daily dosing. The prevalence of postherpetic neuralgia at six months in immunocompetent adults was reduced by 46 percent among ACV-treated patients.

**2.ACV with corticosteroids.** Adults over the age of 50 years given ACV (800 mg PO five times daily for 21 days) and prednisone (60 mg/day PO for the first seven days, 30 mg/day for days 8 to 14 and 15 mg/day for days 15 to 21) have significantly accelerated times to total crusting and total healing. Healthy older adults who have acute herpes zoster associated with significant pain should be treated with ACV plus prednisone.

**B.Valacyclovir (Valtrex).**

**1.**Valacyclovir, the l-valyl ester of ACV, is well absorbed from the gastrointestinal tract and is rapidly converted to ACV in vivo. Valacyclovir is given as 1000 mg PO TID for 7 to 14 days.

**2.**Valacyclovir therapy for 7 or 14 days significantly accelerated the resolution of zoster associated pain compared to ACV (versus 51 days for ACV). Valacyclovir significantly reduced the duration of post herpetic neuralgia (PHN) and decreased the proportion of patients with pain persisting for 6 months compared to ACV.

**C.Famciclovir (Famvir).** Famciclovir, the prodrug of penciclovir, is well absorbed from the gastrointestinal tract and is rapidly converted to the active compound penciclovir. Penciclovir selectively inhibits viral DNA polymerase and

interferes with VZV replication. 500 mg orally three times daily for 7 days.

**D.Recommendation.** Treatment of herpes zoster is recommended for immunocompetent adults under the age of 50 only if they have ophthalmic involvement. Patients over the age of 50 should be treated with an antiviral agent within 72 hours of the appearance of lesions, or for a longer period if new lesions are still developing. Valacyclovir is easier to administer although acyclovir and famciclovir are less expensive. The addition of steroids to any of the antiviral agents can be considered in older patients without a contraindication (eg, osteoporosis, diabetes, hypertension, glaucoma).

**Treatment Options for Herpes Zoster**

| Medication | Dosage |
|---|---|
| Acyclovir (Zovirax) | 800 mg orally five times daily for 7 to 10 days<br>10 mg per kg IV every 8 hours for 7 to 10 days |
| Famciclovir (Famvir) | 500 mg orally three times daily for 7 days |
| Valacyclovir (Valtrex) | 1,000 mg orally three times daily for 7 days |
| Prednisone (Deltasone) | 30 mg orally twice daily on days 1 through 7; then 15 mg twice daily on days 8 through 14; then 7.5 mg twice daily on days 15 through 21 2 (2 to 4) for days 1 through 7<br>2 (1 to 3) for days 8 through 14<br>1 (1 to 2) for days 15 to 21 |

**E.Analgesics.** Mild to moderate pain may respond to over-the-counter analgesics. More severe pain may require a narcotic. Lotions containing calamine (eg, Caladryl) may be used on open lesions to reduce pain and pruritus. Once the lesions have crusted over, capsaicin cream (Zostrix) may be applied. Topical lidocaine (Xylocaine) and nerve blocks have also been reported to be effective in reducing pain.

**F.Ocular involvement.** Ocular herpes zoster is treated with oral antiviral agents and corticosteroids. Ophthalmologic consultation is recommended.

**III.Treatment of postherpetic neuralgia**

**A.**Although postherpetic neuralgia is generally a self-limited condition, it can last indefinitely.

**Treatment Options for Postherpetic Neuralgia**

| Medication | Dosage |
|---|---|
| **Topical agents** | |
| Capsaicin cream (Zostrix) | Apply to affected area three to five times daily. |
| Lidocaine (Xylocaine) patch | Apply to affected area every 4 to 12 hours as needed. |
| **Tricyclic antidepressants** | |
| Amitriptyline (Elavil) | 0 to 25 mg orally at bedtime; increase dosage by 25 mg every 2 to 4 weeks until response is adequate, or to maximum dosage of 150 mg per day. |
| Nortriptyline (Pamelor) | 0 to 25 mg orally at bedtime; increase dosage by 25 mg every 2 to 4 weeks until response is adequate, or to maximum dosage of 125 mg per day. |
| Desipramine (Norpramin) | 25 mg orally at bedtime; increase dosage by 25 mg every 2 to 4 weeks until response is adequate, or to maximum dosage of 150 mg per day. |
| **Anticonvulsants** | |
| Gabapentin (Neurontin) | 100 to 300 mg orally at bedtime; increase dosage by 100 to 300 mg every 3 days until dosage is 300 to 900 mg three times daily or response is adequate. |
| Phenytoin (Dilantin) | 100 to 300 mg orally at bedtime; increase dosage until response is adequate or blood drug level is 10 to 20 µg per mL (40 to 80 µmol per L). |
| Carbamazepine (Tegretol) | 100 mg orally at bedtime; increase dosage by 100 mg every 3 days until dosage is 200 mg three times daily, response is adequate or blood drug level is 6 to12 µg per mL (25.4 to 50.8 µmol per L). |

**B.Analgesics**

**1.**Capsaicin is more efficacious than placebo but must be applied to the affected area three to five times daily. Pain will likely increase during the first few days to a week after capsaicin therapy is initiated.

**2.**Lidocaine patches reduce pain intensity, with minimal systemic absorption. The effect lasts only four to 12 hours with each application.

**3.**Acetaminophen and nonsteroidal anti-inflammatory drugs are useful for potentiating the pain-relieving effects of narcotics.

**C.Tricyclic Antidepressants**

**1.**Tricyclic antidepressants can be effective adjuncts in reducing pain. Tricyclic antidepressants commonly used in the treatment of postherpetic neuralgia include amitriptyline (Elavil), nortriptyline (Pamelor), imipramine (Tofranil) and desipramine (Norpramin).

**2.**The tricyclic antidepressants may cause sedation, dry mouth, postural hypotension, blurred vision and urinary retention. Nortriptyline is better tolerated.

**D.Gabapentin** is effective in treating the pain of postherpetic neuralgia. The dosages required for analgesia are often lower than those used in the treatment of epilepsy.

**E.Transcutaneous electric nerve stimulation** (TENS), biofeedback and nerve blocks are also sometimes used.

**References:** See page 255.

# Syphilis

Syphilis is a sexually transmitted disease (STD) caused by the spirochete *Treponema pallidum*. Despite the overall decreases, outbreaks of syphilis have recently been reported in men who have sex with men. Syphilis is more prevalent in the South, in urban areas, in men, and in blacks.

**I.Stages of syphilis**

**A.**Primary syphilis most often manifests as a solitary, painless chancre that develops at the site of infection three weeks after exposure to *T. pallidum.* Without treatment, blood-borne spread of *T. pallidum* over the next several weeks to months results in secondary syphilis, characterized by fever, lymphadenopathy, diffuse rash, and genital or perineal condyloma latum.

**B.**During the latent stage of syphilis, skin lesions resolve, and patients are asymptomatic. However, serologic tests are positive for *T. pallidum.*

**C.**Tertiary or late syphilis develops years after the initial infection and can involve any organ system. The most dreaded complications are neurosyphilis and involvement of the aortic valve and root.

**II.Diagnosis**

**A.Dark-field microscopy.** Dark-field microscopy is the most specific technique for diagnosing syphilis when an active chancre or condyloma latum is present.

**B.Nontreponemal tests**

**1.**Syphilitic infection leads to the production of nonspecific antibodies that react to cardiolipin. This reaction is the basis of nontreponemal tests such as the VDRL test and rapid plasma reagin test. With nontreponemal tests, false-positive reactions can occur because of pregnancy, autoimmune disorders, and infections. In addition, these tests may show a "prozone" phenomenon in which large amounts of antibody block the antibody-antigen reaction, causing a false-negative test in the undiluted sample.

**2.**Nontreponemal tests are widely used for syphilis screening. However, their usefulness is limited by decreased sensitivity in early primary syphilis and during late syphilis, when up to one third of untreated patients may be nonreactive.

**3.**After adequate treatment of syphilis, nontreponemal tests eventually become nonreactive. However, even with sufficient treatment, patients sometimes have a persistent low-level positive nontreponemal test (referred to as a serofast reaction).

**C.Treponemal-specific tests**

**1.**Treponemal-specific tests detect antibodies to *T. pallidum.* These tests are used to confirm the diagnosis of syphilis in patients with a reactive nontreponemal test. However, the enzyme immunoassay (EIA) test for anti-treponemal IgG also may be used for screening. Treponemal-specific tests include the EIA for anti-treponemal IgG, the *T. pallidum* hemagglutination (TPHA) test, the microhemagglutination test with *T. pallidum* antigen, the fluorescent treponemal antibody-absorption test (FTA-abs), and the enzyme-linked immunosorbent assay.

**2.**Treponemal tests have sensitivities and specificities equal to or higher than those for nontreponemal tests. However, treponemal-specific tests are more difficult and expensive to perform, which limits their usefulness as screening tests. In addition, false-positive results can occur, especially when the FTA-abs test is used in patients with systemic lupus erythematosus or Lyme disease.

**3.**Unlike nontreponemal tests, which show a decline in titers or become nonreactive with treatment, treponemal-specific tests remain reactive for life. Therefore, treponemal-specific test titers are not useful for assessing treatment efficacy.

**III.Primary Syphilis**

**A.**Primary syphilis is most often associated with a single, painless chancre, although it can manifest as multiple chancres, painful papules or ulcers, or no lesions. The chancre is most commonly found on the external genitalia and develops 10 to 90 days (average: 21 days) after infection. Regional lymphadenopathy is common. The chancre usually resolves spontaneously in one to four months.

**B.**Primary syphilis is diagnosed by dark-field microscopy of a suspected lesion or by serologic testing. Either technique can have a false-negative result early in the disease. Thus, if clinical suspicion is high, treatment for syphilis should be initiated.

**Stages of Syphilitic Infection**

| Stag | Clinical | Diagnosis | Treatment |
|---|---|---|---|

| e | manifestations | (sensitivity) | |
|---|---|---|---|
| Primary syphilis | Chancre | Dark-field microscopy of skin lesion (80%)<br>Nontreponemal tests (78% to 86%)<br>Treponemal-specific tests (76% to 84%) | Penicillin G benzathine, 2.4 million units IM (single dose)<br>Alternatives in nonpregnant patients with penicillin allergy: doxycycline (Vibramycin), 100 mg orally twice daily for 2 weeks; tetracycline, 500 mg orally four times daily for 2 weeks; ceftriaxone (Rocephin), 1 g once daily IM or IV for 8 to 10 days; or azithromycin (Zithromax), 2 g orally (single dose) |
| Secondary syphilis | Skin and mucous membranes: diffuse rash, condyloma latum, other lesions<br>Renal system: glomerulonephritis, nephrotic syndrome<br>Liver: hepatitis<br>Central nervous system: headache, meningismus, cranial neuropathy, iritis and uveitis<br>Constitutional symptoms: fever, malaise, generalized lymphadenopathy, arthralgias, weight loss, others | Dark-field microscopy of skin lesion (80%)<br>Nontreponemal tests (100%)<br>Treponemal-specific tests (100%) | Same treatments as for primary syphilis |
| Latent syphilis | None | Nontreponemal tests (95% to 100%)<br>Treponemal-specific tests (97% to 100%) | Early latent syphilis: same treatments as for primary and secondary syphilis<br>Late latent syphilis: penicillin G benzathine, 2.4 million units IM once weekly for 3 weeks<br>Alternatives in nonpregnant patients with penicillin allergy: doxycycline, 100 mg orally twice daily for 4 weeks; or tetracycline, 500 mg orally four times daily for 4 weeks |
| Tertiary (late) syphilis | Gummatous disease, cardiovascular disease | Nontreponemal tests (71% to 73%)<br>Treponemal-specific tests (94% to 96%) | Same treatment as for late latent syphilis |

| | | | |
|---|---|---|---|
| Neuro-syphilis | Seizures, ataxia, aphasia, paresis, hyperreflexia, personality changes, cognitive disturbance, visual changes, hearing loss, neuropathy, loss of bowel or bladder function, others | Cerebrospinal fluid examination | Aqueous crystalline penicillin G, 3 to 4 million units IV every 4 hours for 10 to 14 days; or penicillin G procaine, 2.4 million units IM once daily, plus probenecid, 500 mg orally four times daily, with both drugs given for 10 to 14 days |

**C.**Primary syphilis is treated with 2.4 million units of penicillin G benzathine intramuscularly in a single dose. In nonpregnant patients who are allergic to penicillin, alternative regimens include doxycycline (Vibramycin), 100 mg taken orally twice daily for two weeks, or tetracycline, 500 mg taken orally four times daily for two weeks. Limited evidence indicates that ceftriaxone (Rocephin), in a dosage of 1 g delivered intramuscularly or intravenously once daily for eight to 10 days, or azithromycin (Zithromax), in a single 2-g dose taken orally, may be effective for the treatment of primary syphilis, although close follow-up is warranted.

**D.**At six and 12 months after treatment, patients with primary syphilis should be reexamined and undergo repeat serologic testing. Treatment failure is defined as recurrent or persistent symptoms or a sustained fourfold increase in nontreponemal test titers. Patients with treatment failure should be tested for HIV infection and evaluated for neurosyphilis with a cerebrospinal fluid (CSF) examination.

**IV.Secondary syphilis**

**A.**Secondary syphilis develops several weeks to months after the chancre appears. Patients may present with macular, maculopapular, or even pustular lesions, beginning on the trunk and proximal extremities. The rash of secondary syphilis may involve all skin surfaces, including the palms and soles. Condyloma latum also is associated with secondary syphilis.

**B.**Other organs and systems that can be affected in secondary syphilis include the renal system (glomerulonephritis, nephrotic syndrome), the liver (hepatitis), the CNS (headache, meningitis, cranial neuropathy, iritis, and uveitis), and the musculoskeletal system (arthritis, osteitis, periostitis). Patients also may have fever, malaise, generalized lymphadenopathy, arthralgias, and weight loss.

**C.**The diagnosis of secondary syphilis is confirmed by nontreponemal and treponemal-specific tests. Treatment employs the same antibiotic regimens used for primary syphilis. Follow-up is the same as that for primary syphilis.

**V.Latent syphilis**

**A.**Early latent syphilis encompasses the first year after infection. This stage can be established only in patients who have seroconverted within the past year, who have had symptoms of primary or secondary syphilis within the past year, or who have had a sexual partner with primary, secondary, or early latent syphilis within the past year. Patients who do not meet any of these criteria should be presumed to have late latent syphilis.

**B.**CNS involvement may be asymptomatic. Therefore, the possibility of neurosyphilis should be considered in patients with early or late latent syphilis.

**C.**Early latent syphilis is treated in the same way as primary and secondary syphilis. Late latent syphilis is treated with 2.4 million units of penicillin G benzathine administered intramuscularly once a week for three weeks. Alternative regimens in nonpregnant patients with penicillin allergy include doxycycline, 100 mg taken orally twice daily for four weeks, or tetracycline, 500 mg taken orally four times daily for four weeks.

**D.**After treatment of early or late latent syphilis, quantitative nontreponemal titers should be measured at six, 12, and 24 months. Neurosyphilis should be strongly considered in patients who show a fourfold increase in titers, patients who have an initially high titer (1:32 or greater) that fails to decline at least fourfold, patients who have HIV infection, and patients who develop signs or symptoms of neurosyphilis.

**VI.Tertiary syphilis**

**A.**Tertiary or late syphilis is classified into gummatous syphilis, cardiovascular syphilis, and neurosyphilis. These lesions may affect any organ system but most commonly occur in the skin, mucous membranes, and bones.

**B.**Antibiotic therapy for gummatous and cardiovascular syphilis is the same as that for late latent syphilis, provided no evidence of neurologic involvement is present.

**C.Neurosyphilis at any stage of syphilis**

**1.**Neurologic involvement occurs in up to 10 percent of patients with untreated syphilis. Neurosyphilis should be considered in patients with signs or symptoms of neurologic involvement at any stage of infection and in all patients with late latent or tertiary syphilis, although asymptomatic neurosyphilis is the most common presentation.

**2.**Neurologic involvement also should be suspected in patients who previously have been treated for neurosyphilis, patients who have not responded to treatment for primary, secondary, or latent syphilis, and patients who have HIV infection or other conditions that compromise immune status.

**3.**Lumbar puncture is required to establish the diagnosis of neurosyphilis. The CSF should be tested for white blood cell count and protein level, and for reactivity on a VDRL test.

**References:** See page 255.

## Tuberculosis

Beginning in 1986, an unexpected resurgence of tuberculosis occurred in the United States, with the incidence of the disease rising to 10.5 cases per 100,000 population.

**I.Screening for Tuberculosis**

**A.**Tuberculin testing generally should be performed in persons who belong to at least one of the high-risk groups. Screening should be performed using the Mantoux test (intracutaneous tuberculin test).

**B.**Purified protein derivative (PPD) tuberculin 0.1 mL (5 units) injected intracutaneously, raising a wheal 6 to 10 mm in diameter. After 48 to 72 hours, the test should be "read."

**II.Treatment of Latent Tuberculosis Infection**

**A.**Before initiating treatment of latent tuberculosis infection, physicians must ensure that active disease is not present.

**B.**The usual dosage of isoniazid is 5 mg per kg per day to a maximum of 300 mg per day. A nine-month regimen is recommended. A twice-weekly dosing regimen is acceptable when compliance is in question, but isoniazid should be administered only as directly observed therapy.

**C.**A nine-month course of isoniazid is recommended in children. To reduce the risk of drug-related peripheral neuropathy with isoniazid therapy, pyridoxine (Hexa-Betalin), in a dosage of 10 to 50 mg per day, is coadministered in all children six years of age and older. Pyridoxine should also be strongly considered in patients who have conditions in which neuropathy is common (eg, diabetes, alcoholism and malnutrition), pregnant women and patients who are also taking anticonvulsant drugs.

**Groups at High Risk for Tuberculosis**

- Persons with recent Mycobacterium tuberculosis infection (within the past 2 years) or a history of inadequately treated tuberculosis
- Close contacts of persons known or suspected to have tuberculosis
- Persons infected with the human immunodeficiency virus
- Persons who inject illicit drugs or use other locally identified high-risk substances (eg crack cocaine)
- Residents and employees of high-risk congregate settings (eg correctional institutions, nursing homes, mental institutions or shelters for the homeless)
- Health-care workers who serve high-risk clients
- Foreign-born persons including children who have recently arrived (within 5 years) from countries that have a high incidence or prevalence of tuberculosis (Africa Asia and Latin America)
- Some medically underserved low-income populations
- High-risk racial or ethnic minority populations as defined locally
- Elderly persons
- Children less than 4 years of age or infants children and adolescents who have been exposed to adults in high-risk categories
- Persons with medical conditions known to increase the risk of tuberculosis:
  - Chest radiograph findings suggestive of previous tuberculosis in a person who received inadequate treatment or no treatment
  - Diabetes mellitus
  - Silicosis
  - Organ transplantation
  - Prolonged corticosteroid therapy (eg prednisone in a 15 mg or more per day for 1 month
  - Other immunosuppressive therapy
  - Cancer of the head and neck
  - Hematologic and reticuloendothelial diseases (eg leukemia and lymphoma)
  - End-stage renal disease
  - Intestinal bypass or gastrectomy
  - Chronic malabsorption syndromes
  - Weight that is 10 percent or more below ideal body weight

**Interpretation of the Purified Protein Derivative Tuberculin Skin Test**

I. An induration of 5 mm or more is classified as positive in persons with any of the following:
   A. Human immunodeficiency virus infection
   B. Recent close contact with persons who have active tuberculosis
   C. Chest radiographs showing fibrosis (consistent with healed tuberculosis)

II. An induration of 10 mm or more is classified as positive in all persons who do not meet any of the criteria in section I but have other risk factors for tuberculosis

III. An induration of 15 mm or more is positive in persons who do not meet any of the criteria from sections I or II.

IV. Recent tuberculin skin test conversion is defined as an increase in induration of 10 mm or more within a two-year period, regardless of age.

V. In health-care workers, the recommendations in sections I, II and III generally should be followed. In facilities where tuberculosis patients frequently receive care, the optimal cut-off point for health-care workers with no other risk factors may be an induration of 10 mm or greater.

**D.** Monthly clinical assessments are mandatory in patients taking isoniazid for latent tuberculosis. At each monthly visit, patients should be evaluated for hepatitis, anemia and neurotoxicity.

**E.** Measuring baseline liver enzyme levels before the initiation of isoniazid therapy is recommended only in patients with pregnancy, postpartum status, human immunodeficiency virus infection, alcoholism or chronic hepatitis.

**F.** Isoniazid should be discontinued if transaminase levels are more than three times higher than the upper limit of normal in symptomatic patients or five times higher than the upper limit of normal in asymptomatic patients.

**G.** Regimens for patients exposed to multidrug-resistant tuberculosis generally consist of two drugs to which the infecting organism is likely to be susceptible.

## III. Diagnosis of Active Tuberculosis

**A.** Symptoms of pulmonary tuberculosis, particularly reactivation disease, include cough, fever, sweats, chills, anorexia, weight loss and malaise. Signs of active disease included upper-zone disease on the chest radiograph, fever, night sweats and weight loss, along with a CD4 count of less than 200 cells per $mm^3$ in HIV-infected patients.

**B.** Extrapulmonary tuberculosis may be associated with altered mental status (central nervous system involvement), back pain (spinal disease) and abdominal pain (peritoneal disease). The most common types of extrapulmonary tuberculosis are pleural, lymphatic, bone and joint disease, genitourinary tract and miliary disease, meningitis and peritonitis.

**C.** Although a PPD test should always be performed, it may be negative in 10 to 25 percent of patients with active disease.

**D.** When pulmonary tuberculosis is suspected, chest radiographs should be obtained. In primary pulmonary tuberculosis, numerous abnormalities can be observed, including atelectasis, parenchymal consolidation, lymphadenopathy, pleural effusion and a miliary pattern. Any lung lobe may be affected, although lower-lobe involvement may be somewhat more common. In contrast, reactivation tuberculosis has a predilection for upper-lobe involvement, and cavitation occurs in approximately 50 percent of patients.

**E.** In all patients with suspected active disease, three sputum samples for mycobacterial acid-fast stain examination and Mycobacterium tuberculosis cultures should be collected on each of three consecutive days. Acid-fast smears are usually complete within 24 hours.

## IV. Treatment of Active Tuberculosis

**A.** A four-drug regimen should be initiated in all adults with confirmed or suspected active tuberculosis, and pyridoxine in a dosage of 50 mg per day should be administered with regimens containing isoniazid to help prevent neurotoxicity.

**B.** After two months of a four-drug regimen to which the initial isolates were sensitive, patients continue treatment with isoniazid and rifampin alone if repeat sputum cultures are negative and the patient has improved clinically. Patients continue this dual regimen for another four months, at which time treatment may be discontinued if sputum cultures remain negative. Monthly evaluations, including sputum acid-fast smears and cultures, should be performed throughout treatment.

| Treatment of Active Tuberculosis: First-Line Medications | | | | |
|---|---|---|---|---|
| **Drug** | **Daily dosing** | **Twice-weekly dosing** | **Thrice-weekly dosing** | **Adverse reactions** |
| Isoniazid (INH) | Children: 10 mg per kg PO or IM Adults: 300 mg PO or IM Max: 300 mg Children: 20-40 mg/kg PO/IM | Adults: 15 mg per kg PO or IM Maximum: 300 mg Children: 20 to 40 mg per kg PO or IM | Adults: 15 mg per kg PO or IM Maximum: 300 mg | Elevation of hepatic enzyme levels, hepatitis, neuropathy, central nervous system effects |
| Rifampin (Rifadin) | Children: 10 to 20 mg per kg PO or IV Adults: 10 mg per kg PO or IV Maximum: 600 mg Children: 10 to 20 mg per kg PO or IV | Adults: 10 mg per kg PO or IV Maximum: 600 mg Children: 10 to 20 mg per kg PO or IV | Adults: 10 mg per kg PO or IV Maximum: 600 mg | Orange discoloration of secretions and urine, gastrointestinal tract upset, hepatitis, bleeding problems, flu-like symptoms, drug interactions, rash |

| Drug | Daily dosing | Twice-weekly dosing | Thrice-weekly dosing | Adverse reactions |
|---|---|---|---|---|
| Pyrazinamide | Children: 20 to 30 mg per kg PO Adults: 25 mg per kg PO | Maximum: 2 g Children: 50 to 70 mg per kg PO Adults: 50 to 70 mg per kg PO | Maximum: 4 g Children: 50 to 70 mg per kg PO Adults: 50 to 70 mg per kg PO Maximum: 3 g | Gastrointestinal tract upset, hepatitis, hyperuricemia, arthralgias |
| Ethambutol (Myambutol) | Children and adults: 15 to 25 mg per kg PO | Children and adults: 50 mg per kg PO | Children and adults: 25 to 30 mg per kg PO | Optic neuritis |

| Preferred Initial Treatment of Children and Adults | |
|---|---|
| **Option 1 (daily treatment)** | Administer isoniazid (INH), rifampin (Rifadin), pyrazinamide and ethambutol (Myambutol) daily for 2 months; then administer isoniazid and rifampin daily or two to three times a week (only by directly observed therapy) for susceptible isolates. |
| **Option 2 (twice-weekly treatment)** | Administer isoniazid, rifampin, pyrazinamide and ethambutol daily for 2 weeks; then administer the same drugs two times a week for 6 weeks (only by directly observed therapy); subsequently administer isoniazid and rifampin two times a week for 4 months (only by directly observed therapy) for susceptible isolates. |
| **Option 3 (thrice-weekly treatment)** | Administer isoniazid, rifampin, pyrazinamide and ethambutol three times a week for 6 months (only by directly observed therapy). |

| Selected Regimens for Single-Drug Resistance | | |
|---|---|---|
| **Drug to which infection is resistant** | **Treatment regimen** | **Duration of therapy** |
| Isoniazid (INH) | Rifampin Ethambutol Pyrazinamide | 6 to 9 months |
| Rifampin (Rifadin) | Isoniazid Ethambutol | 18 months |
| Ethambutol (Myambutol), pyrazinamide or streptomycin | Isoniazid Rifampin | 6 to 9 months |

**References:** See page 255.

## Tetanus Prophylaxis

**History of Two Primary Immunizations:**
Low risk wound - Tetanus toxoid 0.5 mL IM.
Tetanus prone - Tetanus toxoid 0.5 mL IM + Tetanus immunoglobulin (TIG) 250-500 U IM.
**Three Primary and 10 yrs since last Booster:**
Low risk wound - Tetanus toxoid, 0.5 mL IM.
Tetanus prone - Tetanus toxoid, 0.5 mL IM.
**Three Primary and 5-10 yrs since last Booster:**
Low risk wound - None
Tetanus prone - Tetanus toxoid, 0.5 mL IM.
**Three Primary and <5 yrs since last Booster:**
Low risk wound - None
Tetanus prone - None

## Infectious Conjunctivitis

Infectious conjunctivitis is one of the most common causes of red eye. The clinical term "red eye" is applied to a variety of infectious or inflammatory diseases of the eye. Conjunctivitis is most frequently caused by a bacterial or viral infection. Sexually transmitted diseases such as chlamydial and gonorrhea are less common causes of conjunctivitis. Ocular allergy is a major cause of chronic conjunctivitis.

**I.Clinical evaluation of conjunctivitis**
**A.**The history should establish whether the condition is acute, subacute, chronic or recurrent, and whether it is unilateral or bilateral.
**B.Discharge**
**1.Serous discharge (watery)** is most commonly associated with viral or allergic ocular conditions.
**2.Mucoid discharge (stringy or ropy)** is highly characteristic of allergy or dry eyes.
**3.Mucopurulent or purulent discharge,** often associated with morning crusting and difficulty opening the eyelids, strongly suggests a bacterial infection. The possibility of *Neisseria gonorrhoeae* infection should be considered when the discharge is copiously purulent.

**C.Itching** is highly suggestive of allergic conjunctivitis. A history of recurrent itching or a personal or family history of hay fever, allergic rhinitis, asthma or atopic dermatitis is also consistent with ocular allergy.

**D.Bilateral conjunctivitis** suggests allergic conjunctivitis. Unilateral conjunctivitis suggests infections caused by viruses and bacteria.

**E.Pain and photophobia** do not usually occur with conjunctivitis, and these findings suggest an ocular or orbital disease processes, including uveitis, keratitis, acute glaucoma or orbital cellulitis. Blurred vision is not characteristic of conjunctivitis and is indicative of corneal or intraocular pathology.

**F.Recent contact with an individual with an upper respiratory tract infection** suggests adenoviral conjunctivitis. Chlamydial or gonococcal infection may be suggested by the sexual history, including a history of urethral discharge.

**Differential Diagnosis of Red Eye**

| | |
|---|---|
| **Conjunctivitis**<br>**Infectious**<br>Viral<br>Bacterial (eg, staphylococcus, Chlamydia)<br>**Noninfectious**<br>Allergic conjunctivitis<br>Dry eye<br>Toxic or chemical reaction<br>Contact lens use<br>Foreign body<br>Factitious conjunctivitis | **Keratitis**<br>**Infectious**. Bacterial, viral, fungal<br>**Noninfectious**. Recurrent epithelial erosion, foreign body<br>**Uveitis**<br>**Episcleritis/scleritis**<br>**Acute glaucoma**<br>**Eyelid abnormalities**<br>**Orbital disorders**<br>Preseptal and orbital cellulitis<br>Idiopathic orbital inflammation (pseudotumor) |

**II.Examination of the eye**

**A.**Visual acuity should be tested before the examination. Regional lymphadenopathy should be sought and the face and eyelids examined. Viral or chlamydial inclusion conjunctivitis typically presents with a tender, preauricular or submandibular lymph node. Palpable adenopathy is rare in acute bacterial conjunctivitis. Herpes labialis or a dermatomal vesicular eruption (shingles) is indicative of a herpetic conjunctivitis.

**B.**Purulent discharge suggests a bacterial infection. Stringy mucoid discharge suggests allergy. Clear watery discharge suggests viral infection.

**III.Cultures and Gram stain** usually are not required in patients with mild conjunctivitis of suspected viral, bacterial or allergic origin. However, bacterial cultures should be obtained in patients who have severe conjunctivitis.

**IV.Treatment of bacterial conjunctivitis**

**A.**Acute bacterial conjunctivitis typically presents with burning, irritation, tearing and a mucopurulent or purulent discharge. The three most common pathogens in bacterial conjunctivitis are *Streptococcus pneumoniae, Haemophilus influenzae* and *Staphylococcus aureus*.

**B.Topical broad-spectrum antibiotics** such as erythromycin ointment and bacitracin-polymyxin B ointment as well as combination solutions such as trimethoprim-polymyxin B provide excellent coverage for most pathogens. Ointments are better tolerated by young children. Solutions are preferred by adults.

**1.Erythromycin ophthalmic ointment**, apply to affected eye(s) q3-4h.

**2.Bacitracin-polymyxin B (Polysporin)** ophthalmic ointment or solution, apply to affected eye(s) q3-4h.

**3.Trimethoprim-polymyxin B (Polytrim)**, ointment or solution, apply to affected eye(s) q3-4h.

**C.Conjunctivitis due to H. influenzae, N. gonorrhoeae, and N. meningitidis** requires systemic antibiotic therapy in addition to topical treatment. Gonococcal conjunctivitis may be treated with ceftriaxone (Rocephin) 1 g IM and topical erythromycin.

**D.Chlamydial conjunctivitis** can be present in newborns, sexually active teenagers, and adults. Diagnosis is by antibody staining of ocular samples. Treatment includes oral tetracycline, doxycycline (Vibramycin) or erythromycin for two weeks.

**V.Viral conjunctivitis**

**A.**Adenovirus is the most common cause of viral conjunctivitis. Viral conjunctivitis often occurs in epidemics, typically presenting with an acutely red eye, watery discharge, conjunctival swelling, a tender preauricular node, photophobia and a foreign-body sensation. Some patients have an associated upper respiratory tract infection.

**B.Treatment** consists of cold compresses and topical vasoconstrictors (Vasocon-A, Naphcon-A). Patients should avoid direct contact with other persons for at least one week after the onset of symptoms.

**C.Ocular herpes simplex** and herpes zoster is managed with topical agents, including trifluridine (Viroptic) and systemic acyclovir, famciclovir or valacyclovir.

**References:** See page 255.

# Gastrointestinal Disorders

## Gastroesophageal Reflux Disease

Gastroesophageal reflux disease is caused by the combination of excess reflux of gastric juice and impaired clearance of this refluxate from the esophagus. GERD is defined as symptoms or tissue damage caused by reflux of gastric contents with or without esophageal inflammation.

**I. Clinical manifestations**

**A.** Typical symptoms of GERD are heartburn and regurgitation; atypical symptoms include odynophagia, dysphagia, chest pain, cough, and reactive airway disease. Up to half of the general population has monthly heartburn or regurgitation.

**B.** Heartburn, the most common symptom of GERD, is a substernal burning sensation that rises from the upper abdomen into the chest and neck. Dysphagia, the sensation that swallowed material is lodged in the chest, may be caused by esophageal inflammation or impaired motility. Esophageal cancer also is an important differential diagnostic consideration when dysphagia is the presenting complaint.

**Symptoms of GERD**

| | |
|---|---|
| Heartburn (pyrosis) | Chronic cough |
| Regurgitation | Nocturnal cough |
| Dysphagia | Asthma |
| Water brash | Dyspepsia |
| Globus | Hiccups |
| Odynophagia | Chest pain |
| Hoarseness | Nausea |

**C.** Chest pain due to GERD can mimic angina. Extraesophageal manifestations of GERD include asthma, chronic cough, sinusitis, pneumonitis, laryngitis, hoarseness, hiccups, and dental disease. Complications of long-standing GERD include esophageal stricture and Barrett's esophagus.

**Differential diagnostic considerations in GERD**

| | |
|---|---|
| Esophageal neoplasm | Nonulcer dyspepsia |
| Infectious esophagitis | Coronary artery disease |
| Caustic esophagitis | Hepatobiliary disease |
| Pill esophagitis | Esophageal motility disorders |
| Gastritis | Cholelithiasis |
| Peptic ulcer disease | |

**II. Diagnosis**

**A.** Diagnosis of GERD is often based on clinical findings and confirmed by the response to therapy. Diagnostic evaluation should be pursued if symptoms are chronic or refractory to therapy or if esophageal or extra-esophageal complications are suspected.

**Indications for esophageal endoscopy in patients with GERD**

Dysphagia or odynophagia
Persistent or progressive symptoms despite therapy
Esophageal symptoms in an immunocompromised patient
Mass, stricture, or ulcer on upper gastrointestinal barium study
Gastrointestinal bleeding or iron deficiency anemia
At least 10 years of GERD symptoms (screen for Barrett's esophagus)

**B.** Ambulatory esophageal pH monitoring is performed by placing a pH electrode just above the lower esophageal sphincter. This test has a sensitivity of 60-100%.

**C.** Short PPI trials are useful for diagnosis of GERD and have a sensitivity of 70 to 90% and specificity of 55 to 85%.

**III. Treatment options**

**A. Lifestyle modification.** Strategies include elevation of the head of the bed 6 to 8 in; reduced consumption of fatty foods, chocolate, alcohol, colas, red wine, citrus juices, and tomato products; avoidance of the supine position after meals; not eating within 3 hours of bedtime; avoidance of tight-fitting clothing; weight loss if obese; and smoking cessation.

**B.** Although $H_2$-blockers are less expensive than PPIs, PPIs provide superior acid suppression, healing rates and symptom relief. Therefore, PPIs may be more cost-effective than $H_2$-blockers, especially in patients with more severe acid-peptic disorders, because of their lower and less frequent dosing requirements and their comparatively shorter duration of required therapy.

**C. Histamine$_2$-blockers** are used extensively. The four available agents, cimetidine (Tagamet), famotidine (Pepcid), nizatidine (Axid), and ranitidine (Zantac), are equivalent. Dosage must be reduced in patients with renal failure. In general, doses of $H_2$ blockers required to control GERD symptoms and heal esophagitis are two to three times higher than those needed for treatment of peptic ulcer disease. Rates of symptom control and healing are about 50%.

**1. Cimetidine (Tagamet)**, 800 mg twice daily; **ranitidine (Zantac)**, 150 mg four times daily; **famotidine (Pepcid)**, 40 mg twice daily; and **nizatidine (Axid)**, 150 mg twice daily.

**D. Proton pump inhibitors (PPIs)** irreversibly bind and inhibit the proton pump.

**1.** The five available PPIs, esomeprazole (Nexium), lansoprazole (Prevacid), omeprazole (Prilosec), pantoprazole (Protonix), and rabeprazole (Aciphex), have

similar pharmacologic activities. PPIs should be taken 20 to 30 minutes before the first meal of the day. PPIs are more effective than are H2 blockers.

**2.**In contrast to the other Proton Pump Inhibitors (PPIs), rabeprazole (Aciphex) forms a partially reversible bond with the proton pump. Therefore, it may have a more sustained acid-suppressing effect than the other PPIs. Rabeprazole and pantoprazole, seem to have fewer drug interactions. Pantoprazole is the least expensive.

| **Proton Pump Inhibitors** | |
|---|---|
| **Drug** | **Dosage** |
| Esomeprazole - *Nexium* | 20 mg or 40 mg, 20 to 30 minutes before the first meal of the day |
| Lansoprazole - *Prevacid* | 30 mg, 20 to 30 minutes before the first meal of the day |
| Omeprazole - *Prilosec*, generic | 20 mg/day, 20 to 30 minutes before the first meal of the day |
| Pantoprazole - *Protonix* | 40 mg PO, 20 minuted before the first meal of the day or IV once daily |
| Rabeprazole - *Aciphex* | 20 mg/day, 20 to 30 minutes before the first meal of the day |

**E.Surgical treatment.** The most common of the antireflux procedures used to treat GERD is the Nissen fundoplication, which is a laparoscopic procedure. A portion of the stomach is wrapped around the distal esophagus. Indications include patient preference for surgical treatment over prolonged medical therapy, incomplete control despite medical therapy, and refractory manifestations of reflux (eg, pneumonia, laryngitis, asthma).

**IV.Management considerations**

**A.**Patients with frequent or unrelenting symptoms or esophagitis, or both, should be treated from the outset with a PPI once or twice daily as appropriate.

**B.Refractory GERD.** Increasing the dosage of PPIs often can control GERD in patients receiving a single daily dose. Sometimes switching to a different PPI can improve symptoms. Antireflux surgical treatment is an alternative.

**Alternative diagnoses in patients with refractory GERD**

Esophageal hypersensitivity (visceral hyperalgesia)
Achalasia
Distal esophageal cancer
Stricture
NSAID-induced symptoms
Infection (eg, Candida, herpes, cytomegalovirus esophagitis)
Caustic exposure
Impaired gastric emptying
Eosinophilic gastroenteritis
Bile acid reflux
Nonulcer dyspepsia
Pill esophagitis

**References:** See page 255.

## *Helicobacter Pylori* Infection and Peptic Ulcer Disease

The spiral-shaped, gram-negative bacterium *Helicobacter pylori* is found in gastric mucosa or adherent to the lining of the stomach. Acute infection is most commonly asymptomatic but may be associated with epigastric burning, abdominal distention or bloating, belching, nausea, flatulence, and halitosis. *H. pylori* infection can lead to ulceration of the gastric mucosa and duodenum and is associated with malignancies of the stomach. The prevalence of *H. pylori* infection is as high as 52 percent.

**I.Pathophysiology**

**A.**Helicobacter pylori (HP), a spiral-shaped, flagellated organism, is the most frequent cause of peptic ulcer disease (PUD). Nonsteroidal anti-inflammatory drugs (NSAIDs) and pathologically high acid-secreting states (Zollinger-Ellison syndrome) are less common causes. More than 90% of ulcers are associated with H. pylori. Eradication of the organism cures and prevents relapses of gastroduodenal ulcers.

**B.Complications of peptic ulcer disease** include bleeding, duodenal or gastric perforation, and gastric outlet obstruction (due to inflammation or strictures).

**II.Clinical evaluation**

**A.Symptoms of PUD** include recurrent upper abdominal pain and discomfort. The pain of duodenal ulceration is often relieved by food and antacids and worsened when the stomach is empty (eg, at nighttime). In gastric ulceration, the pain may be exacerbated by eating.

**B.**Nausea and vomiting are common in PUD. Hematemesis ("coffee ground" emesis) or melena (black tarry stools) are indicative of bleeding.

**C.Physical examination.** Tenderness to deep palpation is often present in the epigastrium, and the stool is often guaiac-positive.

| Presentation of Uncomplicated Peptic Ulcer Disease |
|---|
| Epigastric pain (burning, vague abdominal discomfort, nausea)<br>Often nocturnal<br>Occurs with hunger or hours after meals<br>Usually temporarily relieved by meals or antacids<br>Persistence or recurrence over months to years<br>History of self-medication and intermittent relief |

**D.NSAID-related gastrointestinal complications**. NSAID use and *H pylori* infection are independent risk factors for peptic ulcer disease. The risk is 5 to 20 times higher in persons who use NSAIDs than in the general population. Misoprostol (Cytotec) has been shown to prevent both NSAID ulcers and related complications. The minimum effective dosage is 200 micrograms twice daily; total daily doses of 600 micrograms or 800 micrograms are significantly more effective.

**III.When to test and treat**

**A.**In the absence of alarm symptoms for cancer or complicated ulcer disease, the approach to testing in patients with dyspepsia can be divided into four clinical scenarios: (1) known peptic ulcer disease, currently or previously documented; (2) known nonulcer dyspepsia; (3) undifferentiated dyspepsia, and (4) gastroesophageal reflux disease (GERD).

**B.Peptic ulcer disease.** Treatment of *H. pylori* infection in patients with ulcers almost always cures the disease and reduces the risk for perforation or bleeding.

**C.Nonulcer disease**. There is no convincing evidence that empiric eradication of *H. pylori* in patients with nonulcer dyspepsia improves symptoms.

**D.Undifferentiated dyspepsia.** A test-and-treat strategy is recommended in which patients with dyspepsia are tested for the presence of *H. pylori* with serology and treated with eradication therapy if the results are positive. Endoscopy is reserved for use in patients with alarm signs or those with persistent symptoms despite empiric therapy.

| Alarm Signs for Risk of Gastric Cancer of Complicated Ulcer Disease | |
|---|---|
| Older Than 45 years<br>Rectal bleeding or melena<br>Weight los of >10 percent of body weight<br>Anemia<br>Dysphagia | Abdominal mass<br>Jaundice<br>Family history of gastric cancer<br>Previous history of peptic ulcer<br>Anorexia/early satiety |

| Evaluation for Helicobacter pylori-Related Disease | |
|---|---|
| **Clinical scenario** | **Recommended test** |
| Dyspepsia in patient with alarm symptoms for cancer or complicated ulcer (eg, bleeding, perforation) | Promptly refer to a gastroenterologist for endoscopy. |
| Known PUD, uncomplicated | Serology antibody test; treat if result is positive. |
| Dyspepsia in patient with previous history of PUD not previously treated with eradication therapy | Serology antibody test; treat if result is positive. |
| Dyspepsia in patient with PUD previously treated for *H. pylori* | Stool antigen or urea breath test; if positive, treat with regimen different from the one previously used; retest to confirm eradication. Consider endoscopy. |
| Undifferentiated dyspepsia (without endoscopy) | Serology antibody test; treat if result is positive. |
| Documented nonulcer dyspepsia (after endoscopy) | Unnecessary |
| GERD | Unnecessary |
| Asymptomatic with history of documented PUD not previously treated with eradication therapy | Serology antibody test; treat if result is positive. |
| Asymptomatic | Screening unnecessary |

**E.Gastroesophageal Reflux Disease.** *H. pylori* infection does not increase the risk of GERD. Eradication therapy does not eliminate GERD symptoms (sensation of burning and regurgitation.

**IV.*Helicobacter pylori* Tests**

**A.**Once testing and eradication are chosen, several diagnostic tests are available. Unless endoscopy is planned, a practical approach is to use serology to identify initial infection, and use the stool antigen test or urea breath test to determine cure, if indicated.

**Noninvasive Testing Options for Detecting Helicobacter pylori**

| Test | What does it measure? | Sensitivity | Test of cure? | Comments |
|---|---|---|---|---|
| Serology: laboratory-based ELISA | IgG | 90 to 93 | No | Accurate; convenient for initial infection; titers may remain positive after one year |
| Whole blood: office-based ELISA | IgG | 50 to 85 | No | Less accurate but fast, convenient |
| Stool: HpSA | *H. pylori* antigens | 95 to 98 | Yes | Relatively convenient and available |
| Urea breath test | Urease activity | 95 to 100 | Yes | Sensitivity reduced by acid suppression |

**B.Endoscopy and Biopsy.** Alarm symptoms for cancer or ulcer complication warrant prompt endoscopic evaluation. A gastric antral biopsy specimens is considered the gold standard for detecting the presence of *H. pylori*. Cultures of biopsy specimens obtained during endoscopy can be tested for antimicrobial resistance in cases of treatment failure.

**C.Serology/ELISA.** When endoscopy is not performed, the most commonly used diagnostic approach is the laboratory-based serologic antibody test. This enzyme-linked immunosorbent assay (ELISA) detects IgG antibodies to *H. pylori*, indicating current or past infection. A positive serologic test suggests active infection in patients who have not undergone eradication therapy. The serologic test results may not revert to negative once the organism is eradicated; therefore, the test is not used to identify persistent infection.

**D.Stool testing with enzyme-linked immunoassay** for *H. pylori* antigen in stool specimens is highly sensitive and specific, the stool antigen test reverts to negative from five days to a few months after eradication of the organism, with 90 percent specificity. This test is useful in confirming eradication, and, because it is office-based, is less costly and more convenient than the urea breath test. False-positive results may occur even four weeks following eradication therapy.

**E.Urea Breath Test.** The urea breath test is a reliable test for cure and can detect the presence or absence of active *H. pylori* infection with greater accuracy than the serologic test. It is usually administered in the hospital outpatient setting because it requires time and special equipment.

**V.Principles of treatment**

**A.**Antimicrobial resistance and incomplete treatment are major reasons for treatment failure. Continued therapy for 14 days is the most reliable and effective regimen.

**Triple Therapy Regimens for *Helicobacter pylori* Infection**

| Treatment (10 to 14 days of therapy recommended) | Convenience factor | Tolerability |
|---|---|---|
| **1.** Omeprazole (Prilosec), 20 mg two times daily<br>*or*<br>Lansoprazole (Prevacid), 30 mg two times daily<br>*plus*<br>Metronidazole (Flagyl), 500 mg two times daily<br>*or*<br>Amoxicillin, 1 g two times daily<br>*plus*<br>Clarithromycin (Biaxin), 500 mg two times daily<br>**Prepackaged triple-therapy(Prevpac)**: taken bid for 14 days; consists of 30 mg lansoprazole, 1 g amoxicillin, and 500 mg clarithromycin. | Twice-daily dosing | Fewer significant side effects, but more abnormal taste versus other regimens |
| **2.** Ranitidine bismuth citrate (Tritec), 400 mg twice daily<br>*plus*<br>Clarithromycin, 500 mg twice daily<br>*or*<br>Metronidazole, 500 mg twice daily<br>*plus*<br>Tetracycline, 500 mg twice daily<br>*or*<br>Amoxicillin, 1 g twice daily 92 (RMA) | Twice-daily dosing | Increased diarrhea versus other regimens |

**B.**Triple and quadruple therapies have eradication rates approaching 90 percent or more.

**C.Post-Treatment Followup**

**1.**Routine laboratory testing for cure is not required in patients whose symptoms respond to eradication therapy.

**2.**Routine, noninvasive follow-up testing also can be considered in patients who have persistent symptoms following eradication therapy. In these patients, the stool antigen test, performed four weeks following therapy, is a convenient method. Patients with a history of ulcer complications, gastric mucosa-associated lymphoid tissue (MALT), or early gastric cancer should undergo a routine post-treatment urea breath test or endoscopy to ensure successful eradication.

**D.Treatment of NSAID-related ulcers**

**1.**When the ulcer is caused by NSAID use, healing of the ulcer is greatly facilitated by discontinuing the NSAID. Acid antisecretory therapy with an H2-blocker or proton pump inhibitor speeds ulcer healing. Proton pump inhibitors are more effective in inhibiting gastric acid production and are often used to heal ulcers in patients who require continuing NSAID treatment.

**2.**If serologic or endoscopic testing for H pylori is positive, antibiotic treatment is necessary.

**3.Acute $H_2$-blocker therapy**

**a.Ranitidine (Zantac)**, 150 mg bid or 300 mg qhs.

**b.Famotidine (Pepcid)**, 20 mg bid or 40 mg qhs.

**c.Nizatidine (Axid Pulvules)**, 150 mg bid or 300 mg qhs.

**d.Cimetidine (Tagamet)**, 400 mg bid or 800 mg qhs.

**4.Proton pump inhibitors**

**a.Omeprazole (Prilosec)**, 20 mg qd.

**b.Lansoprazole (Prevacid)**, 15 mg before breakfast qd.

**c.Esomeprazole (Nexium)** 20-40 mg qd.

**d.Pantoprazole (Protonix)** 40 mg PO, 20 minuted before the first meal of the day or IV once daily.

**e.Rabeprazole (Aciphex)** 20 mg/day, 20 to 30 minutes before the first meal of the day.

**VI.Surgical treatment of peptic ulcer disease**

**A.Indications for surgery** include exsanguinating hemorrhage, >5 units transfusion in 24 hours, rebleeding during same hospitalization, intractability, perforation, gastric outlet obstruction, and endoscopic signs of rebleeding.

**B.**Unstable patients should receive a truncal vagotomy, oversewing of bleeding ulcer bed, and pyloroplasty.

**References:** See page 255.

# Constipation

Constipation affects about 2% of the population, occurring more frequently in persons older than 65.

**I.Clinical evaluation**

**A.Diagnostic criteria for constipation (2 or more of the following):**

**1.**Fewer than 3 bowel movements/week.

**2.**Excessive straining during bowel movements.

**3.**A feeling of incomplete evacuation after bowel movements.

**4.**Passage of hard or pellet-like stools.

**B.Clinical evaluation**

**1.**The time of onset of constipation, stool frequency and consistency, the degree of straining, or sensation of incomplete evacuation should be sought.

**2.**Chronic suppression of the urge to defecate contributes to constipation. The amount of fiber and fluid consumed, obstetric, surgical and drug histories, history of back trauma or neurologic problems should be assessed.

**C.Secondary causes of constipation**

**1.**Fissure in ano, hemorrhoids, fistulas, ischiorectal abscess, colonic neoplasms, hypothyroidism, hypercalcemia, diabetes, Hirschsprung's disease, Parkinson's disease, multiple sclerosis, or cerebrovascular disease may cause constipation.

**2.Inadequate fiber** intake commonly causes constipation.

**3.Drugs** that cause constipation include opiate analgesics, aluminum-containing antacids, iron and calcium supplements, antidiarrheals, antihistamines, antidepressants, antiparkinson agents, and calcium channel blockers.

**4.**If secondary causes have been excluded, the most likely cause is idiopathic constipation related to a disorder of colorectal motility.

**D.Physical examination**

**1.**A palpable colon with stool in the left lower quadrant may be detected, although the examination is often normal. Gastrointestinal masses should be sought. Perianal inspection may reveal skin excoriation, skin tags, anal fissures, anal fistula, or hemorrhoids.

**2.**Rectal examination may reveal a mass or stool. Resting and squeeze sphincter tone should be assessed. When the patient is asked to bear down as if to defecate, relaxation of anal tone and perineal descent should be palpable. The absence of anal relaxation or inadequate perineal descent, raises the suspicion of obstructive defecation.

**E.Laboratory evaluation.** A complete blood cell count, glucose, calcium, phosphate, thyroid function test, stool examination for ova and parasites, occult blood, and flexible sigmoidoscopy may be indicated to exclude organic causes.

**II.Empiric management of constipation**

**A.Behavioral modification.** The patient should be encouraged to heed the urge to defecate and not suppress it. Patients should establish a regular pattern of moving their bowels at the same time every day, usually after breakfast. Daily exercise is advised.

**B.Fiber.** The patient should be placed on a diet of 20-30 g of dietary fiber per day. Fiber must be taken with ample fluids.

**C.**Laxatives and nonessential drugs should be discontinued.

**Fiber Preparations**

| Preparation | Recommended Dose | Doses/Day |
|---|---|---|
| **Powder** | | |
| Metamucil (regular) | 1 tsp | 1-3 |
| Metamucil (orange flavor or sugar-free) | 1 tsp | 1-3 |
| | 1 tbsp | 1-3 |
| Citrucel (orange flavor or sugar-free) | 1 tsp | 1-3 |
| Fiberall Natural Flavor | | |
| **Wafers** | | |
| Metamucil | 2 | 1-3 |
| **Tablets** | | |
| Fiberall | 1 | 1-2 |
| **Chewable** | | |
| FiberCon | 2 | 1-4 |

**III.Secondary evaluation**

**A.**If dietary measures are unsuccessful, a secondary evaluation should be undertaken.

**B.Colonoscopy or barium enema** is necessary to rule out an organic lesion.

**C.Assessment of colonic transit time**

**1.The Sitzmarks test** consists of administering a Sitzmarks capsule, containing radiopaque markers. A flat-plate film of the abdomen is obtained 5 days after administration.

**2.**The presence of five or more markers spread out in the colon, suggests slow transit of stool through the colon. If markers are closely clustered in the rectosigmoid segment, this indicates obstructive defecation.

**D.Evaluation of obstructive defecation**

**1.Anorectal manometry.** A pressure probe is placed in the rectum and anus to assesses pressure activity.

**2.Defecography.** Barium is placed in the rectum and the patient bears down during videofluoroscopic imaging.

**3.Electromyograph.** An electrode is placed in the external anal sphincter and myoelectrical activity is measured.

**4.Simulated defecation.** A silicone-filled artificial stool is placed in the rectum. Difficulty in expelling the artificial stool indicates obstructive defecation.

**IV.Treatment of refractory constipation**

**A.Saline cathartics**, such as magnesium-containing compounds and phosphate enemas, work by an osmotic effect. Magnesium or phosphate overload may occur in renal insufficiency. Long-term use is not recommended. **Magnesium hydroxide** (1-2 tbsp qd-bid) is most commonly used. In refractory cases, a half to 1 glassful of **magnesium citrate** is effective.

**B.Lactulose** is a hyperosmotic non-absorbable sugar that is often used for long-term management. Its advantages are nonsystemic absorption, minimal toxicity, and safety for prolonged use; 30 mL PO qd-bid. Sorbitol is less expensive than lactulose; the 70% solution is taken as 30 mL qd-bid.

**C.Lavage solutions (CoLyte, GoLYTELY)** are used for refractory constipation. These agents contain a balanced electrolyte solution. A gallon should be administered in 4 hours to relieve an impaction. Eight to16 oz a day can prevent recurrence.

**D.Combination therapy** with an osmotic agent combined with a lavage solution may be used for refractory constipation.

**E.Enemas** may relieve severe constipation. Low-volume tap water enemas or sodium phosphate (Fleet) enemas can be given once a week to help initiate a bowel movement.

**F.Stool impaction.** A combination of suppositories (glycerin or bisacodyl) and enemas (phosphate) will soften the stool. Digital disimpaction may be necessary should these measures fail.

**G.Surgery.** When the above measures are not effective, surgical options may include colectomy and ileostomy or an ileoanal pouch.

**References:** See page 255.

## Acute Diarrhea

Acute diarrhea is defined as diarrheal disease of rapid onset, often with nausea, vomiting, fever, and abdominal pain. Most episodes of acute gastroenteritis will resolve within 3 to 7 days.

**I.Clinical evaluation of acute diarrhea**

**A.**The nature of onset, duration, frequency, and timing of the diarrheal episodes should be assessed. The appearance of the stool, buoyancy, presence of blood or mucus, vomiting, or pain should be determined.

**B.**Contact with a potential source of infectious diarrhea should be sought.

**C.Drugs that may cause diarrhea** include laxatives, magnesium-containing compounds, sulfa-drugs, and antibiotics.

**II.Physical examination**

**A.Assessment of volume status.** Dehydration is suggested by dry mucous membranes, orthostatic hypotension, tachycardia, mental status changes, and acute weight loss.

**B.Abdominal tenderness**, mild distention and hyperactive bowel sounds are common in acute infectious diarrhea. The presence of rebound tenderness or rigidity suggests toxic megacolon or perforation.

**C.Evidence of systemic atherosclerosis** suggests ischemia. Lower extremity edema suggests malabsorption or protein loss.

**III.Acute infectious diarrhea**

**A.Infectious diarrhea** is classified as noninflammatory or inflammatory, depending on whether the infectious organism has invaded the intestinal mucosa.

**B.Noninflammatory** infectious diarrhea is caused by organisms that produce a toxin (enterotoxigenic E coli strains, Vibrio cholerae). Noninflammatory, infectious diarrhea is usually self-limiting and lasts less than 3 days.

**C.Blood or mucus** in the stool suggests inflammatory disease, usually caused by bacterial invasion of the mucosa (enteroinvasive E coli, Shigella, Salmonella, Campylobacter). Patients usually have a septic appearance and fever; some have abdominal rigidity and severe abdominal pain.

**D.Vomiting out of proportion to diarrhea** is usually related to a neuroenterotoxin-mediated food poisoning from Staphylococcus aureus or Bacillus cereus, or rotavirus (in an infant), or Norwalk virus (in older children or adults). The incubation period for neuroenterotoxin food poisoning is less than 4 hours, while that of a viral agent is more than 8 hours.

**E.Traveler's diarrhea** is a common acute diarrhea. Three or four unformed stools are passed/per 24 hours, usually starting on the third day of travel and lasting 2-3 days. Anorexia, nausea, vomiting, abdominal cramps, abdominal bloating, and flatulence may also be present.

**F.Antibiotic-related diarrhea**

**1.**Antibiotic-related diarrhea ranges from mild illness to life-threatening pseudomembranous colitis. Overgrowth of Clostridium difficile causes pseudomembranous colitis. Amoxicillin, cephalosporins and clindamycin have been implicated most often, but any antibiotic can be the cause.

**2.**Patients with pseudomembranous colitis have high fever, cramping, leukocytosis, and severe, watery diarrhea. Latex agglutination testing for C difficile toxin can provide results in 30 minutes.

**3.Enterotoxigenic E coli**

**a.**The enterotoxigenic E coli include the E coli serotype 0157:H7. Grossly bloody diarrhea is most often caused by E. coli 0157:H7, causing 8% of grossly bloody stools.

**b.**Enterotoxigenic E coli can cause hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, intestinal perforation, sepsis, and rectal prolapse.

**IV.Diagnostic approach to acute infectious diarrhea**

**A.**An attempt should be made to obtain a pathologic diagnosis in patients who give a history of recent ingestion of seafood (Vibrio parahaemolyticus), travel or camping, antibiotic use, homosexual activity, or who complain of fever and abdominal pain.

**B.**Blood or mucus in the stools indicates the presence of Shigella, Salmonella, Campylobacter jejuni, enteroinvasive E. coli, C. difficile, or Yersinia enterocolitica.

**C.**Most cases of mild diarrheal disease do not require laboratory studies to determine the etiology. In moderate to severe diarrhea with fever or pus, a stool culture for bacterial pathogens (Salmonella, Shigella, Campylobacter) is submitted. If antibiotics were used recently, stool should be sent for Clostridium difficile toxin.

**V.Laboratory evaluation of acute diarrhea**

**A.Fecal leukocytes** is a screening test which should be obtained if moderate to severe diarrhea is present. Numerous leukocytes indicate Shigella, Salmonella, or Campylobacter jejuni.

**B.Stool cultures for bacterial pathogens** should be obtained if high fever, severe or persistent (>14 d) diarrhea, bloody stools, or leukocytes is present.

**C.Examination for ova and parasites** is indicated for persistent diarrhea (>14 d), travel to a high-risk region, gay males, infants in day care, or dysentery.

**D.Blood cultures** should be obtained prior to starting antibiotics if severe diarrhea and high fever is present.

**E.E coli 0157:H7 cultures.** Enterotoxigenic E coli should be suspected if there are bloody stools with minimal fever, when diarrhea follows hamburger consumption, or when hemolytic uremic syndrome is diagnosed.

**F.Clostridium difficile cytotoxin** should be obtained if diarrhea follows use of an antimicrobial agent.

**G.Rotavirus antigen test (Rotazyme)** is indicated for hospitalized children <2 years old with gastroenteritis. The finding of rotavirus eliminates the need for antibiotics.

**VI.Treatment of acute diarrhea**

**A.Fluid and electrolyte resuscitation**

**1.Oral rehydration.** For cases of mild to moderate diarrhea in children, Pedialyte or Ricelyte should be administered. For adults with diarrhea, flavored soft drinks with saltine crackers are usually adequate.

**2.Intravenous hydration** should be used if oral rehydration is not possible.

**B.Diet**. Fatty foods should be avoided. Well-tolerated foods include complex carbohydrates (rice, wheat, potatoes, bread, and cereals), lean meats, yogurt, fruits, and vegetables. Diarrhea often is associated with a reduction in intestinal lactase. A lactose-free milk preparation may be substituted if lactose intolerance becomes apparent.

**VII.Empiric antimicrobial treatment of acute diarrhea**

**A.Febrile dysenteric syndrome**

**1.**If diarrhea is associated with high fever and stools containing mucus and blood, empiric antibacterial therapy should be given for Shigella or Campylobacter jejuni.

**2.**Norfloxacin (Noroxin) 400 mg bid **OR**

**3.**Ciprofloxacin (Cipro) 500 mg bid.

**B.Travelers' diarrhea**. Adults are treated with norfloxacin 400 mg bid, ciprofloxacin 500 mg bid, or ofloxacin 300 mg bid for 3 days.

**References:** See page 255.

# Chronic Diarrhea

Diarrhea is considered chronic if it lasts longer than 2 weeks.

**I.Clinical evaluation of chronic diarrhea**

**A.**Initial evaluation should determine the characteristics of the diarrhea, including volume, mucus, blood, flatus, cramps, tenesmus, duration, frequency, effect of fasting, stress, and the effect of specific foods (eg, dairy products, wheat, laxatives, fruits).

**B.Secretory diarrhea**

**1.**Secretory diarrhea is characterized by large stool volumes (>1 L/day), no decrease with fasting, and a fecal osmotic gap <40.

**2.Evaluation of secretory diarrhea** consists of a giardia antigen, Entamoeba histolytica antibody, Yersinia culture, fasting serum glucose, thyroid function tests, and a cholestyramine (Cholybar, Questran) trial.

**C.Osmotic diarrhea**

**1.**Osmotic diarrhea is characterized by small stool volumes, a decrease with fasting, and a fecal osmotic gap >40. Postprandial diarrhea with bloating or flatus also suggests osmotic diarrhea. Ingestion of an osmotically active laxative may be inadvertent (sugarless gum containing sorbitol) or covert (with eating disorders).

**2.Evaluation of osmotic diarrhea**

**a.**Trial of lactose withdrawal.

**b.**Trial of an antibiotic (metronidazole) for small-bowel bacterial overgrowth.

**c.**Screening for celiac disease (anti-endomysial antibody, antigliadin antibody).

**d.**Fecal fat measurement (72 hr) for pancreatic insufficiency.

**e.**Trial of fructose avoidance.

**f.**Stool test for phenolphthalein and magnesium if laxative abuse is suspected.

**g.**Hydrogen breath analysis to identify disaccharidase deficiency or bacterial overgrowth.

**D.Exudative diarrhea**

**1.**Exudative diarrhea is characterized by bloody stools, tenesmus, urgency, cramping pain, and nocturnal occurrence. It is most often caused by inflammatory bowel disease, which may be suggested by anemia, hypoalbuminemia, and an increased sedimentation rate.

**2.Evaluation of exudative diarrhea** consists of a complete blood cell count, serum albumin, total protein, erythrocyte sedimentation rate, electrolyte measurement, Entamoeba histolytica antibody titers, stool culture, Clostridium difficile antigen test, ova and parasite testing, and flexible sigmoidoscopy and biopsies.

**References:** See page 255.

# Anorectal Disorders

**I.Hemorrhoids**

**A.**Hemorrhoids are dilated veins located beneath the lining of the anal canal. Internal hemorrhoids are located in the upper anal canal. External hemorrhoids are located in the lower anal canal.

**B.**The most common symptom of internal hemorrhoids is painless rectal bleeding, which is usually bright red and ranges from a few drops to a spattering stream at the end of defecation. If internal hemorrhoids remain prolapsed, a dull aching may occur. Blood and mucus stains may appear on underwear, and itching in the perianal region is common.

**Classification of Internal Hemorrhoids**

| Grade | Description | Symptoms |
|---|---|---|
| 1 | Non-prolapsing | Minimal bleeding |
| 2 | Prolapse with straining, reduce when spontaneously prolapsed | Bleeding, discomfort, pruritus |
| 3 | Prolapse with straining, manual reduction required when prolapsed | Bleeding, discomfort, pruritus |
| 4 | Cannot be reduced when prolapsed | Bleeding, discomfort, pruritus |

**C.Management of internal hemorrhoids**

**1.Grade 1 and uncomplicated grade 2 hemorrhoids** are treated with dietary modification (increased fiber and fluids).

**2.Symptomatic grade 2 and grade 3 hemorrhoids**. Treatment consists of hemorrhoid banding with an anoscope. Major complications are rare and consist of excessive pain, bleeding, and infection. Surgical hemorrhoidectomy may sometimes be necessary.

**3.Grade 4 hemorrhoids** require surgical hemorrhoidectomy.

**D.External hemorrhoids**

**1.**External hemorrhoids occur most often in young and middle-aged adults, becoming symptomatic only when they become thrombosed.

**2.**External hemorrhoids are characterized by rapid onset of constant burning or throbbing pain, accompanying a new rectal lump. Bluish skin-covered lumps are visible at the anal verge.

**3.Management of external hemorrhoids**

**a.**If patients are seen in the first 48 hours, the entire lesion can be excised in the office. Local anesthetic is infiltrated, and the thrombus and overlying skin are excised with scissors. The resulting wound heals by secondary intention.

**b.**If thrombosis occurred more than 48 hours prior, spontaneous resolution should be permitted to occur.

**II.Anal fissures**

**A.**An anal fissure is a longitudinal tear in the distal anal canal, usually in the posterior or anterior midline. Patients with anal fissures complain of perirectal pain which is sharp, searing or burning and is associated with defecation. Bleeding from anal fissures is bright red and not mixed with the stool.

**B.**Anal fissures may be associated with secondary changes such as a sentinel tag, hypertrophied anal papilla, induration of the edge of the fissure, and anal stenosis. Crohn's disease should be considered if the patient has multiple fissures, or whose fissure is not in the midline.

**C.**Anal fissures are caused by spasm of the internal anal sphincter. Risk factors include a low-fiber diet and previous anal surgery.

**D.Treatment of anal fissures**

**1.**High-fiber foods, warm sitz baths, stool softeners (if necessary), and daily application of 1% hydrocortisone cream to the fissure should be initiated. These simple measures may heal acute anal fissures within 3 weeks in 90% of patients.

**2.Lateral partial internal sphincterotomy** is indicated when 4 weeks of medical therapy fails. The procedure consists of surgical division of a portion of the internal sphincter, and it is highly effective. Adverse effects include incontinence to flatus and stool.

**III.Levator ani syndrome and proctalgia fugax**

**A.**Levator ani syndrome refers to chronic or recurrent rectal pain, with episodes lasting 20 minutes or longer. Proctalgia fugax is characterized by anal or rectal pain, lasting for seconds to minutes and then disappearing for days to months.

**B.**Levator ani syndrome and proctalgia fugax are more common in patients under age 45, and psychological factors are not always present.

**C.**Levator ani syndrome is caused by chronic tension of the levator muscle. Proctalgia fugax is caused by rectal muscle spasm. Stressful events may trigger attacks of proctalgia fugax and levator ani syndrome.

**D.Diagnosis and clinical features**

**1.**Levator ani syndrome is characterized by a vague, indefinite rectal discomfort or pain. The pain is felt high in the rectum and is sometimes associated with a sensation of pressure.

**2.**Proctalgia fugax causes pain that is brief and self limited. Patients with proctalgia fugax complain of sudden onset of intense, sharp, stabbing or cramping pain in the anorectum.

**3.**In patients with levator ani syndrome, palpation of the levator muscle during digital rectal examination usually reproduces the pain.

**E.Treatment**

**1.Levator ani syndrome.** Treatment with hot baths, nonsteroidal anti-inflammatory drugs, muscle relaxants, or levator muscle massage is recommended. EMG-based biofeedback may provide improvement in pain.

**2.Proctalgia fugax.** For patients with frequent attacks, physical modalities such as hot packs or direct anal pressure with a finger or closed fist may alleviate the pain. Diltiazem and clonidine may provided relief.

**IV.Pruritus ani**

**A.**Pruritus ani is characterized by the intense desire to scratch the skin around the anal orifice. It occurs in 1% of the population. Pruritus ani may be related to fecal leakage.

**B.**Patients report an escalating pattern of itching and scratching in the perianal region. These symptoms may be worse at night. Anal hygiene and dietary habits, fecal soiling, and associated medical conditions should be sought.

**C.**Examination reveals perianal maceration, erythema, excoriation, and lichenification. A digital rectal examination and anoscopy should be performed to assess the sphincter tone and look for secondary causes of pruritus. Patients who fail to respond to 3 or 4 weeks of conservative treatment should undergo further investigations such as skin biopsy and sigmoidoscopy or colonoscopy.

**D.Treatment and patient education**

**1.**Patients should clean the perianal area with water following defecation, but avoid soaps and vigorous rubbing. Following this, the patient should dry the anus with a hair dryer or by patting gently with cotton. Between bowel movements a thin cotton pledget dusted with unscented cornstarch should be placed against the anus. A high fiber diet is recommended to regulate bowel movements and absorb excess liquid. All foods and beverages that exacerbate the itching should be eliminated.

**2.**Topical medications are not recommended because they may cause further irritation. If used, a bland cream such as zinc oxide or 1% hydrocortisone cream should be applied sparingly two to three times a day.

**3.**Diphenhydramine (Benadryl) or hydroxyzine (Vistaril) may relieve the itching and allow the patient to sleep.

**V.Perianal abscess**

**A.**The anal glands, located in the base of the anal crypts at the level of the dentate line, are the most common source of perianal infection. Acute infection causes an abscess, and chronic infection results in a fistula.

**B.**The most common symptoms of perianal abscess are swelling and pain. Fevers and chills may occur. Perianal abscess is common in diabetic and immunosuppressed patients, and there is often a history of chronic constipation. A tender mass with fluctuant characteristics or induration is apparent on rectal exam.

**C.Management of perianal abscess**. Perianal abscesses are treated with incision and drainage using a local anesthetic. Large abscesses require regional or general anesthesia. A cruciate incision is made close to the anal verge and the corners are excised to create an elliptical opening which promotes drainage. An antibiotic, such as Zosyn, Timentin, or Cefotetan, is administered.

**D.**About half of patients with anorectal abscesses will develop a fistula tract between the anal glands and the perianal mucosa, known as a fistula-in-ano. This complication manifests as either incomplete healing of the drainage site or recurrence. Healing of a fistula-in-ano requires a surgical fistulotomy.

**References:** See page 255.

# *Neurologic Disorders*

## Migraine Headache

Migraine affects 15% to 17% of women and 6% of men. Headaches can generally be grouped into three major categories: migraine, tension-type, and organic.

**I.Clinical evaluation**

**A.Migraine** headaches are usually unilateral, and the acute attack typically lasts from 4 to 24 hours. Migraine headaches can occur with an aura or without an aura. The aura may consist of focal neurologic symptoms starting 5 to 30 minutes before onset of an acute headache attack.

**B.**The most common aura symptoms associated with migraine include scotomata (blind spots), teichopsia (fortification spectra, or the sensation of a luminous appearance before the eyes), photopsia (flashing lights), and paresthesias, as well as visual and auditory hallucinations, diplopia, ataxia, vertigo, syncope, and hyperosmia.

**C.Tension-type headache** is characterized by steady, aching pain of mild to moderate intensity, often as a band-like pain around the head. Gastrointestinal and neurologic signs and symptoms usually do not occur.

**D.Physical examination** should assess the fundus of the eye, neck rigidity, and identify infectious processes of the nose and throat. The temporal artery may appear dilated and pulsating. Neurologic symptoms should be evaluated with computed tomographic scanning.

**Features of Migraine Headache and Headache Caused by Underlying Disease**

| Migraine headache | Headache caused by serious underlying disease |
|---|---|
| **History** | |
| • Chronic headache pattern similar from attack to attack<br>• Gastrointestinal symptoms<br>• Aura, especially visual<br>• Prodrome | • Onset before puberty or after age 50 (tumor)<br>• "Worst headache ever" (subarachnoid hemorrhage)<br>• Headache occurring after exertion, sex, or bowel movement (subarachnoid hemorrhage)<br>• Headache on rising in the morning (increased intracranial pressure, tumor)<br>• Personality changes, seizures, alteration of consciousness (tumor)<br>• Pain localized to temporal arteries or sudden loss of vision (giant cell arteritis)<br>• Very localized headache (tumor, subarachnoid hemorrhage, giant cell arteritis) |

| Migraine headache | Headache caused by serious underlying disease |
|---|---|
| **Physical examination** | |
| • No signs of toxicity<br>• Normal vital signs<br>• Normal neurologic examination | • Signs of toxicity (infection, hemorrhage)<br>• Fever (sinusitis, meningitis, or other infection)<br>• Meningismus (meningitis)<br>• Tenderness of temporal arteries (giant cell arteritis)<br>• Focal neurologic deficits (tumor, meningitis, hemorrhage)<br>• Papilledema (tumor) |
| **Laboratory tests and neuroimaging** | |
| • Normal results | • Erythrocyte sedimentation rate >50 mm/hr (giant cell arteritis)<br>• Abnormalities on lumbar puncture (meningitis, hemorrhage)<br>• Abnormalities on CT or MRI (tumor, hemorrhage, aneurysm) |

## II. Pathophysiology of migraine

**A.** Migraine headache is probably generated by a nucleus in the brainstem. The central generator is the contralateral dorsal raphe nucleus of the midbrain. After the dorsal raphe central generator turns on, there is an activation of the trigeminovascular system. This system connects the generator to the meningeal blood vessels, which dilate and become inflamed, a process referred to as neurogenic inflammation.

**B.** Two key serotonin (5-HT) receptors, 5-$HT_{1B}$ and 5-$HT_{1D}$, reverse the migraine processes. The 5-$HT_{1D}$ receptors are vasoconstrictive and are located in the lumen of the meningeal vessels.

## III. Treatment of migraine

### A. 5-$HT_{1D}$ receptor agonists ("Triptans")

#### 1. Rizatriptan (Maxalt)

**a.** Rizatriptan (Maxalt) is a high-efficacy, quick-onset triptan, like sumatriptan and zolmitriptan. Oral bioavailability is more than 40%.

**b.** Rizatriptan has two doses, 5 and 10 mg, and two forms, traditional tablet and mint-flavored, orally dissolvable tablet or melt. Two-hour headache response for the optimal dose (10 mg) is 67-77%. Recurrence rate is 30-47%.

**c.** The melt is not absorbed through the buccal mucosa, but rather dissolves on the tongue, is swallowed, and then is absorbed in the gastrointestinal tract. Its efficacy is the same as the traditional tablet, with a two-hour headache response of 66-74%. Adverse events for rizatriptan are similar to those seen with sumatriptan and zolmitriptan tablets.

**d.** Propranolol raises the circulating rizatriptan level, so patients on propranolol should be given the 5-mg rizatriptan dose. Others should take the 10-mg dose. The maximum rizatriptan dose is 30 mg per 24 hours, but 15 mg per 24 hours for patients on propranolol.

#### 2. Almotriptan (Axert)

**a.** Almotriptan works as well as sumatriptan; however, it is better tolerated. Almotriptan causes less chest pain than sumatriptan; however, it remains contraindicated in patients with ischemic heart disease or uncontrolled hypertension as are all triptans. It comes in 6.25 and 12.5 mg tablets.

**b.** Most patients should take 12.5 mg at the onset of a migraine. Patients with hepatic or renal impairment should start with 6.25 mg. Patients should not take more than 2 doses in 24 hours.

#### 3. Sumatriptan (Imitrex)

**a.** Sumatriptan (Imitrex) is available in three forms: subcutaneous injection, nasal spray, and oral tablet. Injectable sumatriptan comes as a 6 mg dose for use with an autoinjector. Subcutaneous sumatriptan is the most effective triptan. It works extremely quickly with 50% headache response at 30 minutes, a one-hour headache response of 77%, and more than 80% at two hours. Recurrence of migraine within 24 hours after a headache response with injectable sumatriptan is 34-38%. Recurrence with the spray and tablet is 35-40%.

**b. Nasal spray sumatriptan.** 20 mg is the optimal dose, with a two-hour headache response of 64%. Almost 40% have headache response at 30 minutes. The spray comes in a single-use device. When sniffed, it causes a terrible taste in the back of the throat; therefore, patients should spray it once in one nostril and not sniff in.

**c.** The sumatriptan oral tablet has a bioavailability of 14%. The optimal starting dose is 50 mg, with a 61% headache response at two hours.

**d.** Maximum sumatriptan dosages are two 6-mg subcutaneous doses, two 20-mg nasal sprays, or four 50-mg tablets per 24 hours. However, if a patient needs to switch, she can use one injection or one spray plus two tablets in the same day, or one injection plus one spray in 24 hours.

**e.** All triptans can cause subjective "triptan sensations," which include heat feelings and flushing, numbness, paresthesias, tiredness and tightening, and heaviness of neck, jaw, and chest. Triptans can narrow coronary arteries. These drugs are contraindicated in coronary artery disease, vascular dis-

ease, uncontrolled hypertension, basilar or hemiplegic migraine or within 24 hours of another triptan or ergot.

**f.**Sumatriptan is the most used triptan. The injection has the fastest onset for a triptan, and the highest overall efficacy.

**4.Zolmitriptan (Zomig)**

**a.**Zolmitriptan has an oral bioavailability of 40%. Zolmitriptan is contraindicated with MAO-A inhibitors. The optimal dose is 2.5 mg. The maximum dose is 10 mg per 24 hours. Two-hour headache response is 62-65%. Recurrence rate averages about 30%. Adverse events are triptan sensations, similar to sumatriptan tablets.

**b.**Zolmitriptan is superior to oral sumatriptan (50 mg) for headache response at two hours, 67.1% vs. 63.8%, respectively. Zolmitriptan has a longer duration of action than sumatriptan.

**5.Naratriptan (Amerge)** has good oral bioavailability (63-74%) and a longer T 1/2 (6 hours) than sumatriptan. It works more slowly, and in a lower percentage of patients, than the other three triptans. Two-hour headache response for the optimal dose of 2.5 mg is 48%. The maximum dose is 5 mg per 24 hours. Naratriptan should not be used in patients with rapid onset migraine or who wake up with migraine. Naratriptan should only be selected for those patients who are sensitive to side effects.

**6.Frovatriptan (Frova)** has the longest half-life (26 hours compared to 6 hours or less for the others). It has a slow onset and is less effective than the other triptans. Frova comes in 2.5 mg tablets. Patients start with one tablet and can repeat after 2 hours if the headache recurs; maximum 3 tabs in 24 hours.

**7.Eletriptan (Relpax)** appears to be at least as effective as oral sumatriptan for acute treatment of migraine. Eletriptan interacts with CYP3A4 inhibitors, including verapamil, which is used for migraine prophylaxis. Initial dosage is 20 or 40 mg, which can be repeated after 2 hours if headache improves and then recurs. The maximum dosage is 80 mg in 24 hours.

**8.Triptan selection**

**a.**Patients with migraine should receive a triptan as the first-line medication. If they have significant nausea, an oral drug is not recommended. Rather, a parenteral or nasal spray sumatriptan should be used.

**b.**Most patients should initially be treated with rizatriptan (Maxalt) or almotriptan (Axert). Other agents may be used if the patient requires a faster onset, longer duration, or fewer side effects.

**c.**Sumatriptan provides the greatest versatility in multiple forms to allow a patient various modes of treatment. The 6-mg subcutaneous injection offers the greatest speed and the highest efficacy of any triptan.

**d.Rizatriptan (Maxalt)** tends to be faster and more effective than oral sumatriptan with a similar incidence of adverse effects.

**e.Almotriptan (Axert)** seems to work about as well as sumatriptan, but it's better tolerated.

**f.Zolmitriptan (Zomig)** has similar efficacy and tolerability compared to sumatriptan.

**g.Naratriptan (Amerge)** has a slower onset and is less effective, but this agent is better tolerated.

**h.Frovatriptan (Frova)** has the longest half-life (26 hours compared to 6 hours or less for the others). It has a slow onset and is less effective than the other triptans.

**Drugs for Treatment of Migraine and Tension Headache**

| Drug | Dosage |
|---|---|
| **5-HT$_1$ Receptor Agonists ("Triptans")** | |
| Rizatriptan (Maxalt) | 5- or 10-mg tablet or wafer (MLT); can be repeated in 2 hours; max 100 mg/day,<br>5 mg/day in patients on propranolol |
| Almotriptan (Axert) | 12.5 mg at the onset of a migraine. Patients with hepatic or renal impairment should start with 6.25 mg. Max 2 doses per day. |
| Sumatriptan (Imitrex) | 6 mg SC; can be repeated in 1 hour; max 2 injections/day<br>50 mg PO; can be repeated in 2 hours; max 100 mg<br>20 mg intranasally; can be repeated after 2 hours; max 40 mg/day<br>Max in combination: two injections or sprays; or one of either plus two tablets |
| Naratriptan (Amerge) | 2.5-mg tablet, can be repeated 4 hours later; max 5 mg/day |
| Zolmitriptan (Zomig, Zomig-ZMT, Zomig nasal spray) | 2.5-5 mg PO; can be repeated in 2 hours. Tablets and orally disintegrating tablets, 2.5, 5 mg.<br>Intranasally 5 mg; can be repeated after 2 hours; max 10 mg/day |
| Frovatriptan (Frova) | 2.5 mg PO, repeat after 2 hours if the headache recurs; max 3 tabs in 24 hours. Longest half-life, slow onset, less effective |

| Drug | Dosage |
|---|---|
| Eletriptan (Relpax) | 20 or 40 mg, repeated after 2 hours if headache recurs; max 80 mg in 24 hours. |
| **NSAIDs** | |
| Ibuprofen (Motrin) | 400-800 mg, repeat as needed in 4 hr |
| Naproxen sodium (Anaprox DS) | 550-825 mg, repeat as needed in 4 hr |
| **Ergot Alkaloids** | |
| Dihydroergotamine DHE 45<br><br>Migranal Nasal Spray | 1 mg IM; can be repeated twice at 1-hour intervals (max 3 mg/attack)<br>1 spray (0.5 mg)/nostril, repeated 15 minutes later (2 mg/dose; max 3 mg/24 hours) |
| Ergotamine 1 mg/caffeine 100 mg (Ercaf, Gotamine, Wigraine) | 2 tablets PO, then 1 q30min, x 4 PRN (max 6 tabs/attack) |
| **Butalbital combinations** | |
| Aspirin 325 mg, caffeine 40 mg, butalbital 50 mg (Fiorinal) | 2 tablets, followed by 1 tablet q4-6h as needed |
| **Isometheptene combination** | |
| Isometheptene 65 mg, acetaminophen 325 mg, dichloralphenazone 100 mg (Midrin) | 2 tablets, followed by 1 tablet as needed q4-6h prn |
| **Opioid Analgesics** | |
| Butorphanol (Stadol NS) | One spray in one nostril; can be repeated in the other nostril in 60-90 minutes; the same two-dose sequence can be repeated in 3 to 5 hours |

**B.Prophylaxis against migraine**

**1.**Patients with frequent or severe migraine headaches or those refractory to symptomatic treatment may benefit from prophylaxis. Menstrual or other predictable migraine attacks may sometimes be prevented by a brief course of an NSAID, taken for several days before and during menstruation.

**2.Beta-adrenergic blocking agents** are used most commonly for continuous prophylaxis. Propranolol, timolol, metoprolol (Lopressor), nadolol (Corgard) and atenolol (Tenormin) have been effective.

**3.Tricyclic antidepressants** can prevent migraine and may be given with other prophylactic agents. Amitriptyline (Elavil) in a dosage ranging from 10 to 50 mg qhs is commonly used.

**4.Valproate (Depakote)**, an anticonvulsant, has been effective in decreasing migraine frequency. Its effectiveness is equal to that of propranolol. Adverse effects include nausea, weight gain and fatigue.

| Drugs for Prevention of Migraine | |
|---|---|
| **Drug** | **Dosage** |
| Propranolol (Inderal) | 80 to 240 mg/day, divided bid, tid or qid |
| Timolol (Blocadren) | 10 to 15 mg bid |
| Divalproex (Depakote) | 250 mg bid |
| Amitriptyline (Elavil) | 25-50 mg qhs |

**References:** See page 255.

# Vertigo

The clinical evaluation of vertigo begins with the patient's description of symptoms and the circumstances in which they occur. Many drugs can cause dizziness. Common nonvestibular causes (eg, hyperventilation, orthostatic hypotension, panic disorder) are often diagnosed.

**I.History and physical examination**

**A.**Patients may use the term "dizziness" to describe one or more different sensations. These sensations include vertigo (spinning), light-headedness, unsteadiness and motion intolerance. The onset of symptoms, whether the sensation is constant or episodic, how often episodes occur and the duration of episodes should be assessed. Activities or movements that provoke or worsen a patient's dizziness should be sought as well as activities that minimize symptoms. Rotational vertigo when rolling over in bed is highly suggestive of BPPV.

**B.**Vertigo is a sensation of movement of the self or of one's surroundings. Patients may describe vertigo as a sensation of floating, giddiness or disorientation. The duration of vertiginous symptoms and whether head movement

provokes symptoms (positional vertigo) or if attacks occur without provocation (spontaneous vertigo) should be assessed.

**C.**Hearing loss, tinnitus and aural fullness should be sought. Vision, strength and sensation, coordination, speech and swallowing should be evaluated. Double vision or hemiplegia strongly suggest a central nervous system lesion rather than a peripheral vestibular disorder. History for cardiac disease, migraine, cerebrovascular disease, thyroid disease and diabetes should be sought.

**Drugs Associated with Dizziness**

| Class of drug | Type of dizziness | Mechanism |
|---|---|---|
| Alcohol | Positional vertigo | Specific-gravity difference in endolymph vs cupula |
| Intoxication | CNS depression | Disequilibrium<br>Cerebellar dys-function |
| Tranquilizers | Intoxication | CNS depression |
| Anticonvulsants | Intoxication<br>Disequilibrium | CNS depression<br>Cerebellar dys-function |
| Antihypertensives | Near faint | Postural hypotension |
| Aminoglycosides | Vertigo<br>Disequilibrium<br>Oscillopsia | Asymmetric hair-cell loss<br>Vestibulospinal reflex loss<br>Vestibulo-ocular reflex loss |

**D.Physical examination** should evaluate orthostatic blood pressure changes followed by a complete head and neck examination as well as otologic and neurologic examinations. A pneumatic otoscope should be used to confirm normal tympanic membrane mobility. Balance, gait, cerebellar and cranial nerve function, and nystagmus should be evaluated.

**E.Nystagmus** consists of involuntary eye movements caused by asymmetry of signals from the right and left vestibular systems. Nystagmus of peripheral vestibular origin is usually horizontal with a slight or dramatic rotary component. Nystagmus of central origin is usually predominantly vertical.

**F.The Dix-Hallpike test** is particularly helpful to elicit nystagmus associated with BPPV. This maneuver stimulates the posterior semicircular canal, which is the semicircular canal most commonly involved in BPPV.

**G.An audiogram** should be performed if a specific cause of dizziness cannot be found after a thorough history and physical examination. Additional testing may include electronystagmography, auditory evoked brainstem response testing, radiologic imaging of the brain, brainstem and temporal bone and selected blood tests. Auditory evoked brainstem response testing measures the integrity of the auditory system and is useful to screen for acoustic tumors. Magnetic resonance imaging (MRI) should be reserved for patients with unilateral otologic symptoms or neurologic symptoms or those in whom dizziness persists despite appropriate treatment.

**II.Benign paroxysmal positional vertigo**

**A.**The most common cause of peripheral vestibular vertigo is BPPV. This condition is characterized by sudden, brief and sometimes violent vertigo after a change in head position. The sensation of vertigo usually lasts for only a few seconds. This form of vertigo is often noticed when a patient lies down, arises or turns over in bed. BPPV does not cause hearing loss, ear fullness or tinnitus. BPPV can occur at any age but is most commonly seen in elderly persons. Although usually unilateral, bilateral BPPV occurs in up to 15 percent of patients. Nystagmus is characteristic of BPPV.

**B.**BPPV is caused by displacement of otoconia from the utricle or saccule into the posterior semicircular canal. Therefore, when a patient moves the head into a provocative position, the otoconia provoke movement of the endolymphatic fluid inside the semicircular canal, creating a sensation of vertigo.

**C.**Treatment of BPPV. In-office physical therapy, known as repositioning maneuvers, redirects displaced otoconia into the utricle. This form of treatment is effective in 85 to 90 percent of patients. Another type of exercise that is performed at home also attempts to redirect displaced otoconia and is effective in 60 to 70 percent of patients.

**D.**During these exercises, the patient initially sits upright on the edge of a bed or couch. Then the patient rapidly lies down on his side with the affected ear down. Vertigo usually occurs. After the vertigo subsides (or after one minute if no vertigo occurs), the patient rapidly turns in a smooth arc to the opposite side. After vertigo associated with this movement subsides (or after one minute if no vertigo occurs), the patient slowly sits upright. The entire maneuver is repeated five times twice per day until the patient no longer experiences vertigo for two successive days. Surgical treatment is reserved for the 2 to 5 percent of cases that fail to respond to nonsurgical treatment.

**III.Vestibular neuronitis**

**A.**Vestibular neuronitis is characterized by acute onset of intense vertigo associated with nausea and vomiting that is unaccompanied by any neurologic or audiologic symptoms. The symptoms usually reach their peak within 24 hours and then gradually subside. During the first 24 to

48 hours of a vertiginous episode, severe truncal unsteadiness and imbalance are present.

**B.** Vestibular neuronitis is presumed to have a viral etiology because it is often associated with a recent history of a flu-like illness. Management of the initial stage of vestibular neuronitis includes bed rest and the use of antiemetics (eg, promethazine [Phenergan]) and vestibular suppressants (eg, diazepam [Valium]). After the patient is able to stand, the brain begins compensating for the acute loss of unilateral vestibular function. The compensation process may be enhanced by performance of vestibular exercises twice per day for eight to 10 weeks.

**IV. Meniere's disease**

**A.** Meniere's disease is characterized by fluctuating hearing loss, tinnitus, episodic vertigo and, occasionally, a sensation of fullness or pressure in the ear. Vertigo rapidly follows and is typically severe, with episodes occurring abruptly and without warning. The duration of vertigo is usually several minutes to hours. Unsteadiness and dizziness may persist for days after the episode of vertigo.

**B.** Diseases with similar symptoms include syphilis, acoustic neuroma and migraine. Isolated episodes of hearing loss or vertigo may precede the characteristic combination of symptoms by months or years.

**C.** Meniere's disease results from excessive accumulation of endolymphatic fluid (endolymphatic hydrops). As inner-ear fluid pressure increases, symptoms of Meniere's disease develop.

**D.** Diuretics (eg, triamterene-hydrochlorothiazide [Dyazide, Maxzide]) and a low-salt diet are the mainstays of treatment. This combined regimen reduces endolymphatic fluid pressure. Other preventive measures include use of vasodilators and avoidance of caffeine and nicotine. Acute vertiginous episodes may be treated with oral or intravenous diazepam. Promethazine or glycopyrrolate (Robinul) is effective in the treatment of nausea.

**E.** Surgical treatments are an option when appropriate prophylactic measures fail to prevent recurrent episodes of vertigo. Surgical procedures used in the treatment of Meniere's disease range from draining excess endolymphatic fluid from the inner ear (endolymphatic shunt) to severing the vestibular nerve (with hearing preservation). In selected cases, a chemical labyrinthectomy may be performed. Chemical labyrinthectomy involves the injection of a vestibulotoxic gentamicin (Garamycin) solution into the middle ear.

**Antivertiginous and Antiemetic Drugs**

| Classes and agents | Dosage | Comments |
|---|---|---|
| **Antihistamines** | | |
| Dimenhydrinate (Benadryl) | 50 mg PO q4-6h or 100-mg supp. q8h | Available without prescription, mild sedation, minimal side effects |
| Meclizine (Antivert) | 25-50 mg PO q4-6h | Mild sedation, minimal side effects |
| Promethazine (Phenergan) | 25-50 mg PO, IM, or suppository q4-6h | Good for nausea, vertigo, more sedation, extrapyramidal effects |
| **Monoaminergic agents** | | |
| Amphetamine | 5 or 10 mg PO q4-6h | Stimulant, can counteract sedation of antihistamines, anxiety |
| Ephedrine | 25 mg PO q4-6h | Available without prescription |
| **Benzodiazepine** | | |
| Diazepam (Valium) | 5 or 10 mg PO q6-8h | Sedation, little effect on nausea |
| **Phenothiazine** | | |
| Prochlorperazine (Compazine) | 5-25 mg PO, IM, or suppository q4-6h | Good antiemetic; extrapyramidal side effects, particularly in young patients |

**References:** See page 255.

## Seizure Disorders and Epilepsy

Epilepsy is a disorder that consists of recurrent seizures. Epilepsy occurs in 1 to 2 percent of the general population. The incidence of epilepsy is highest in infancy. It decreases during childhood and is lowest in adolescence. The incidence markedly increases in elderly patients.

**I. Clinical evaluation**

**A.** Epileptic seizures are behavioral changes resulting from paroxysmal, excessive electrical discharges from the brain. Not all jerks, shakes, and episodic behaviors are seizures. For example, tics, tremors, dystonia, and attention-deficit disorder can imitate epileptic seizures.

**B.** Once a paroxysmal behavioral event is identified as a seizure, the next step is to determine whether it is epilepsy or a secondary effect of hypoxia, hypoglycemia, infection, fever, and toxic substance abuse (eg, alcohol withdrawal, cocaine use). Epilepsy is characterized by recurrent seizures (ie, at least two seizures are needed for diagnosis).

**C.** Epilepsy can result from either inherited or acquired factors. Head injury, stroke, brain tumor, cortical dysplasia, and infection are common causes of both seizures. In many cases, the cause of epilepsy remains unknown.

**II. Features of epileptic seizures**

**A.** Epileptic seizures are divided into two broad categories--generalized and partial. Generalized seizures arise from both sides of the brain simultaneously. Partial (ie, focal) seizures occur within one or more restricted regions of the brain.

**Nonepileptic paroxysmal disorders that can mimic epileptic seizure**

Syncope
- Reflex (vasovagal, carotid sinus, glossopharyngeal, cough)
- Decreased cardiac output
- Decreased left ventricular filling (hypovolemia, orthostatic hypotension, pulmonary embolism)
- Cardiac arrhythmia

Migraine with auras, basilar migraine, confusional migraine
Transient ischemic attack
Periodic paralysis
Sleep disorders (parasomnias, daytime amnestic episodes)
Gastrointestinal disorders (reflux, motility disorders)
Movement disorders (tics, Tourette's syndrome, nonepileptic myoclonus, paroxysmal choreoathetosis, shuddering attacks)
Psychiatric disorders (panic, somatization, dissociation, conversion [nonepileptic psychogenic seizures])
Drug toxicity and substance abuse
Breath-holding spells

**Classification of epileptic seizures**

| Generalized | Partial |
|---|---|
| Absence | Simple partial (consciousness not impaired) |
| Myoclonic | Complex partial (consciousness impaired) |
| Tonic | Partial with secondary generalization (can be tonic-clonic, tonic, or clonic) |
| Atonic | |
| Clonic | |
| Tonic-clonic (grand mal seizure) | |

**A.** Partial seizures are further classified as simple, complex, or secondarily generalized. Simple partial seizures alter behavior but do not impair consciousness. Complex partial seizures alter consciousness. Partial seizures can also become secondarily generalized, causing tonic and clonic movements.

**B. History of the event.** A witnessed, 90-second episode that involved loss of consciousness, stiffening, and jerking of the extremities followed by muscle soreness, headache, and the need to sleep for several hours afterwards strongly suggests a tonic-clonic seizure.

**History of a suspected seizure**

**Before the event**
Unusual stress (eg, severe emotional trauma)
Sleep deprivation
Recent illness
Unusual stimuli (eg, flickering lights)Use of medications and drugs
Activity immediately before event (eg, change in posture, exercise)

**During the event**
Symptoms at onset (eg, aura)
Temporal mode of onset: gradual versus sudden
Duration: brief (ictal phase <5 min) versus prolonged
Stereotypy: duration and features of episodes nearly identical versus frequently changing
Time of day: related to sleep or occurring on awakening
Ability to talk and respond appropriately
Ability to comprehend
Ability to recall events during the seizure
Abnormal movements of the eyes, mouth, face, head, arms, and legs
Bowel or bladder incontinence
Bodily injury

**After the event**
Confusion
Lethargy
Abnormal speech
Focal weakness or sensory loss (ie, Todd's paralysis)
Headache, muscle soreness, or physical injury

**C. A witness should answer the following questions:**

**1.** What was the patient doing at the onset? Did the event begin with arrested speech, odd behavior, or repetitive actions? Evidence of any focal rhythmic behavior of the face or extremities at the onset suggests partial epilepsy.

**2.** What was the patient doing during the event? Signs may include: tonic movements or posturing seen as stiffening, most often of the extremities or axial body; clonic movements; a rhythmic flexion-extension movement of the extremities; loss of consciousness; incontinence; and tongue biting.

**3.** What was the duration of the ictal event? This information can differentiate true seizure from psychogenic events, which often last longer.

**4.** What was the patient doing after the ictal event? Focal deficits and Todd's paralysis are common findings. The presence of postictal confusion may help differentiate between seizure and syncope.

**III. Past medical history**

**A.** Meningitis, encephalitis, head trauma, cancer, or cerebrovascular disease suggests the cause of epilepsy focus. In diabetic patients, hypoglycemia (glucose less than

40 mg/dL) or hyperglycemia (glucose higher than 300 mg/dL) may precipitate seizures. Hyponatremia, hypocalcemia, hypomagnesemia, hypoparathyroidism, hypothyroidism also may cause seizures.

**B.Medications.** Theophylline, meperidine (Demerol), isoniazid, antipsychotic drugs (clozapine [Clozaril], phenothiazines), radiocontrast dyes, alkylating agents, and beta-lactam antibiotics are among the most commonly implicated medications in seizure. Other medications include lidocaine, anesthetics, tricyclic antidepressants, selective serotonin reuptake inhibitors, bupropion (Wellbutrin), acyclovir (Zovirax), beta-blockers, and decongestants (eg, phenylpropanolamine). Seizures can be provoked by alcohol withdrawal, cocaine, phencyclidine (PCP), and 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy").

**IV.Physical examination**

**A.Findings** may include trauma, infection, malignancy, congenital anomalies, and focal weakness or spasticity suggesting previous stroke.

**B.Vital signs** should be measured and a general medical examination performed.

**1.**Examine the patient for injuries from the seizure or fall.

**2.**Check oxygen saturation and auscultate the chest for aspiration.

**3.**Measure heart rhythm and rate, blood pressure, and orthostatic changes for assessment of syncope.

**4.**Auscultate for carotid murmurs or carotid bruits and sources of embolic stroke.

**5.**Check for rapid pulses, which are often present after seizure and may help in evaluation of psychogenic seizures.

**C.Neurologic examination**

**1.**Patients should be observed for fluency of language, facial asymmetry, gaze preferences, and pupillary asymmetry. The last presents in patients who have herniation from brain swelling caused by parenchymal or epidural bleeding and in those who have a rapidly growing brain tumor.

**2.**Sensory deficits suggest parietal lobe dysfunction. An extensor plantar response may be noted after a seizure and is not necessarily a pathologic finding.

**V.Diagnostic testing**

**A.Measurement of glucose, calcium, magnesium,** thyroid hormone, liver enzyme levels, and toxicology screening (including blood alcohol levels) may reveal common medical causes of seizures. A complete blood cell count may suggest infection, anemia, or sickle cell disease.

**B.Lumbar puncture** should be performed in patients suspected to have had an infection or a fever after assessment of the possible risks of the procedure (eg, coagulopathy, mass lesion). Patients who are immunocompromised because of corticosteroid use, recent transplantation or HIV infection should undergo cerebrospinal fluid evaluation to detect possible fungal, bacterial, or viral infection.

**C.Computed tomography** can detect the presence of bleeding or gross structural lesions immediately after a seizure. However, magnetic resonance imaging is the study of choice because it is more sensitive and specific for evaluating structural lesions.

**D.Electroencephalogram (EEG)** can help establish the presence and type of epilepsy, although its value is limited. An estimated 0.4% of adults and 2.8% of children who have never had a seizure may have interictal epileptiform discharges. A normal EEG does not refute the diagnosis of epilepsy. The initial EEG reveals epileptiform activity in only 40% of the patients with probable epilepsy. The yield of the test is enhanced by using sleep deprivation, hyperventilation, and photic stimulation.

**E.Ambulatory 24-hour EEG recordings** can be useful for patients in whom epileptic seizure is a relatively strong possibility when the standard EEG is normal.

**VI.Treatment of epilepsy**

**A.**After a single tonic-clonic seizure, recurrence rates are 15 to 60%. After two tonic-clonic seizures, the risk of a third seizure is 85%.

**B.**Treatment should be started with one drug and then increase the dose gradually until the patient is seizure-free or experiences significant side effects.

**Initial treatment for partial and generalized epilepsies**

| Type of epilepsy | First-line agents | Second-line agents |
|---|---|---|
| **Partial** | Carbamazepine, oxcarbazepine (Trileptal), phenytoin (Dilantin) | Divalproex (Depakote), felbamate (Felbatol), gabapentin (Neurontin), lamotrigine (Lamictal), levetiracetam (Keppra), tiagabine (Gabitril Filmtabs), topiramate (Topamax), valproate (Depakene), zonisamide (Zonegran) |
| **Generalized** | | |
| Absence seizures | Ethosuximide (Zarontin), valproate | Lamotrigine, levetiracetam |
| Idiopathic | Lamotrigine, valproate | Topiramate, zonisamide |

| Type of epilepsy | First-line agents | Second-line agents |
|---|---|---|
| Symptom-atic | Lamotrigine, topiramate, valproate, zonisamide | Barbiturates, benzodiazepines |

**VII.Therapy for localization-related partial epilepsy**

**A.**About 70% of adult patients with epilepsy have partial-onset seizures, which encompass simple partial, complex partial, and secondarily generalized tonic-clonic seizures. About 50% of patients have both partial seizures and secondarily generalized tonic-clonic seizures.

**B.**For the majority of patients with newly diagnosed partial epilepsy, initial treatment consists of carbamazepine (Tegretol), oxcarbazepine (Trileptal), or phenytoin (Dilantin). Alternative choices include divalproex (Depakote), felbamate (Felbatol), gabapentin (Neurontin), lamotrigine (Lamictal), levetiracetam (Keppra), tiagabine (Gabitril), topiramate (Topamax), and zonisamide (Zonegran).

**Antiepileptic Drugs**

| | Adult dosage | Children (per kg of body weight) | Dosing intervals |
|---|---|---|---|
| Carbamazepine (Tegretol) | 600 to 1,600 mg | 20 to 40 mg | Three or four times per day |
| Ethosuximide (Zarontin) | 750 to 1,5000 mg | 4 to 5 mg | Twice per day |
| Gabapentin (Neurontin) | 900 mg up to 6,000 mg | | Three or four times per day |
| Lamotrigine (Lamictal) | 200 to 800 mg | | Twice per day |
| Levetiracetam (Keppra). | 500 and 1500 mg | | Once or twice per day |
| Phenobarbital (Solfoton) | 1 to 4 mg per kg | 2 to 5 mg | Once or twice per day |
| Phenytoin (Dilantin) | 200 to 500 mg | 5 mg up to a maximum of 300 mg | Once or twice per day |
| Primidone (Mysoline) | 500 to 1,000 mg | 10 to 20 mg | Three or four times per day |
| Tiagabine (Gabitril Filmtabs) | 32 to 56 mg | | Three or four times per day |
| Topiramate (Topamax) | 400 to 800 mg | | Twice per day |
| Valproic acid (Depakene, Depakote) | 15 to 60 mg per kg | 15 to 60 mg | Three or four times per day |
| Zonisamide (Zonegran) | 100 and 600 mg per day | | Once per day |

**C.Carbamazepine (Tegretol)** usual starting dose is 200 mg twice per day, with weekly increases of 200 mg per day and a usual daily maintenance dose of 600 to 1,200 mg. The long-acting formulations of carbamazepine improve compliance because they can be taken twice daily and are better tolerated. Carbamazepine is a strong inducer of some of hepatic cytochrome P-450 and is associated with a number of significant drug-drug interactions. In addition, carbamazepine induces its own metabolism. The usual therapeutic range for serum carbamazepine levels is 6 to 12 mg/L.

**D.Oxcarbazepine (Trileptal)** is approved for initial monotherapy. This drug has significant efficacy as monotherapy in patients newly diagnosed as having partial epilepsy as well as patients whose condition is refractory. Oxcarbazepine is more tolerable and associated with less frequent rashes than carbamazepine. Oxcarbazepine is initiated at 150 mg twice a day, with weekly increments of 300 mg per day and a target dose of 900 to 1,200 mg. Compared with carbamazepine, oxcarbazepine is associated with substantially fewer drug-drug interactions and does not undergo autoinduction.

**E.Phenytoin (Dilantin),** the usual starting dose is 300 mg daily (4 to 5 mg/kg per day), with a maintenance dose of 200 to 500 mg per day. A loading dose of phenytoin at 18 to 20 mg/kg can be given orally or intravenously. Phenytoin can be given once daily, although it is often administered two or three times per day to minimize side effects. The therapeutic serum range of phenytoin is 10 to 20 mg/L. Phenytoin is a strong hepatic enzyme inducer and is prone to drug-drug interactions.

**F.Divalproex (Depakote)** is usually started at 250 to 500 mg twice daily (10 to 15 mg/kg per day), with weekly increments of 250 to 500 mg per day (5 to 10 mg/kg per day) and a range in daily dose from 1,000 to 3,000 mg. An intravenous formulation is available. The therapeutic serum range is 50 to 150 mg/L.

**G.Monotherapy versus polytherapy**

**1.**About 47% of patients with newly diagnosed epilepsy became seizure-free during treatment with their first AED and 14% became seizure-free during treatment with a second or third drug.

**2.Felbamate (Felbatol)** is an effective drug, but its use has been severely restricted because of its association with life-threatening aplastic anemia and fulminant hepatic failure. It should not be used as first-line therapy.

**3.Gabapentin (Neurontin)** has the advantages of safety, tolerability, favorable pharmacokinetic profile, and ease of use. It has been used mostly as adjunctive therapy in patients with refractory seizures but is an attractive agent as monotherapy in patients with severe hepatic disease, cutaneous allergies, porphyria, or acquired immunodeficiency disease and in elderly patients who take a number of medications. The effective dose is 900 to 4,800 mg per day, divided into three doses.

**4.Lamotrigine (Lamictal)** is approved as adjunctive therapy and as second-line monotherapy. It is sometimes used as initial monotherapy because it has a similar efficacy as phenytoin or carbamazepine and is better tolerated than carbamazepine.

**5.Tiagabine (Gabitril)** exerts its effect by inhibiting the reuptake of g-aminobutyric acid. It has efficacy two times daily or four times daily. This drug is used as adjunctive therapy, with a usual starting dose of 4 mg per day, weekly increments of 4 mg per day, and a target daily dose between 32 and 64 mg.

**6.Topiramate (Topamax)** has significant efficacy when used as adjunctive therapy. Because of potential adverse cognitive events, it should be started at a low dose, with gradual adjustment. Starting dose is 25 or 50 mg per day with weekly increments of 25 to 50 mg per day. The usual target dose for adjunctive therapy is 400 mg taken twice daily, with a dose range between 100 and 1,000 mg per day.

**7.Levetiracetam (Keppra)** is an attractive AED because of tolerability and ease of use. The starting dose is 500 mg at bedtime, with weekly increments of 500 mg and a total target daily dose between 1,000 and 3,000 mg divided into two doses. It can be used in monotherapy.

**8.Zonisamide (Zonegran)** is approved as adjunctive therapy. It should be avoided in patients with sulfa allergies. Zonisamide can be associated with a rash in 3%; rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis, can occur. The recommended starting dose is 100 mg taken once a day, with increments of 100 mg every 2 weeks if needed, with a target dose between 100 and 600 mg per day.

**VIII.Therapy for generalized epilepsies**

**A.**For patients who have multiple seizure types, it is necessary to choose a broad-spectrum anticonvulsant with efficacy against multiple seizure types.

**B.**Valproate remains a mainstay treatment for these patients, but lamotrigine, topiramate, and zonisamide, are also efficacious against multiple seizure types and can be considered as alternative agents. Because of its tolerability, some physicians select lamotrigine rather than valproate as the initial drug of choice.

**IX.Discontinuation of therapy.** Patients who remain seizure-free for at least 2 years should be considered candidates for tapering and discontinuing AED treatment. About two-thirds of patients remain seizure-free following discontinuation of treatment.

**References:** See page 255.

# Alzheimer's Disease

Alzheimer's disease currently affects about 4 million people in the United States. This neurodegenerative disease causes selective neuronal loss in brain regions involved in memory, language, personality, and cognition. The earliest symptom of Alzheimer's disease is usually the insidious onset and progression of memory loss. Initially, this memory loss can be difficult to differentiate from common age-associated benign forgetfulness. However, patients with age-associated benign forgetfulness are aware of the deficit and their activities of daily living are minimally impaired.

**I.Pathogenesis**

**A.**Age is the major risk factor for development of Alzheimer's disease. The incidence of Alzheimer's disease increases with age, doubling every 5 years between ages 60 and 85. Limited education and a history of head trauma may also be factors in development of disease.

**B.**The presenilin 1 gene is the most common site of mutations responsible for early-onset Alzheimer's disease. Genetic testing should be restricted to patients with early-onset Alzheimer's disease and a strong family history of dementia.

**C.**Onset of dementia symptoms after age 60 occurs in about 90% of patients with Alzheimer's disease.

**II.Diagnosis**

| **Criteria for diagnosis of Alzheimer's disease** |
|---|
| Dementia established by clinical examination and documented by the Mini-Mental State Examination or similar examination |
| Deficits in two or more areas of cognition (ie, language, memory, perception) |
| Progressive worsening of memory and other cognitive function; as disease progresses, patient experiences impairment in activities of daily living and altered behavioral patterns |
| No disturbance of consciousness |
| Onset between ages 40 and 90, but most often after age 65 |
| Absence of other systemic disorder or brain disease that may account for deficits in memory and cognition |

**A.** Computed tomographic scanning and magnetic resonance imaging often show generalized and hippocampal atrophy in patients with Alzheimer's disease. These tests are not sensitive enough to establish a diagnosis. Imaging is useful in excluding a diagnosis of stroke, tumor, or hydrocephalus.

**B.** Delirium should be excluded and coexisting conditions that worsen dementia by reviewing medications, screening for depression, and ruling out nutritional deficiencies, diabetes mellitus, uremia, alterations in electrolytes and thyroid disease.

**III. Treatment of Cognitive Deficits in Alzheimer's Disease**

**A. Cholinesterase Inhibitors.** Treatment with cholinesterase inhibitors can provide modest improvement of symptoms, temporary stabilization of cognition, or reduction in the rate of cognitive decline in mild to moderate Alzheimer's disease. Approximately 20 to 35 percent exhibit a seven-point improvement on neuropsychologic tests (5 to 15 percent benefit). These agents raise acetylcholine levels in the brain by inhibiting acetylcholinesterase.

**Cholinesterase Inhibitors for the Treatment of Mild-to-Moderate Alzheimer's Disease**

| Drug | Dosage | Side effects | Specific cautions |
|---|---|---|---|
| Donepezil (Aricept) | Initial dosage is 5 mg once daily; if necessary, dosage can be increased to 10 mg once daily after 4 to 6 weeks. | Mild side effects, including nausea, vomiting, and diarrhea; effects can be reduced by taking with food. Initial increase of agitation in some; agitation subsides after a few weeks. | Possible interactions with cimetidine (Tagamet), theophylline, warfarin (Coumadin), and digoxin (Lanoxin) |
| Rivastigmine (Exelon) | Initial dosage of 1.5 mg bid (3 mg per day) is well tolerated; dosage can be increased as tolerated to maximum of 6 mg twice daily (12 mg per day). | Nausea, vomiting, diarrhea, headaches, dizziness, abdominal pain, fatigue, malaise, anxiety, and agitation; these effects can be reduced by taking rivastigmine with food. | Weight loss Interacting drugs include aminoglycosides and procainamide (Procanbid). |
| Galantamine (Reminyl) | Initial dosage is 4 mg bid (8 mg per day) for 4 weeks; dosage is then increased to 8 mg twice daily (16 mg per day) for at least 4 weeks. An increase to 12 mg twice daily (24 mg per day) should be considered. | Mild side effects, including nausea, vomiting, and diarrhea; these effects can be reduced by taking galantamine with food. No apparent association with sleep disturbances (which can occur with other cholinergic treatments) | Contraindicated for use in patients with hepatic or renal impairment |
| Tacrine (Cognex) | Initial dosage is 10 mg four times daily (40 mg per day) for 4 weeks. | High incidence of side effects, including gastrointestinal problems. | Hepatotoxicity is a problem; hence, liver tests should be performed. |

**1. Donepezil (Aricept)** is given once daily, beginning with a dosage of 5 mg per day, which can be increased to 10 mg per day (max) after four weeks. Donepezil is not hepatotoxic. Adverse effects are mild (eg, nausea, vomiting, and diarrhea) and are reduced when taken with food. An initial increase in agitation may occur, which subsides after the first few weeks. Donepezil produces improvements of cognitive and global function with mild-to-moderate Alzheimer's disease.

**2. Rivastigmine (Exelon)** is initiated in a dosage of 1.5 mg twice daily. The dosage is increased by 1.5 mg twice daily (3 mg per day) as tolerated, every four weeks, to a maximum of 6 to 12 mg per day. No laboratory monitoring is required. Adverse effects include nausea, vomiting, diarrhea, weight loss, headaches, dizziness, abdominal pain, fatigue, malaise, anxiety, and agitation. Rivastigmine has been is effective in temporarily slowing cognitive decline, improving function, and reducing behavioral and psychopathologic symptoms in mild-to-moderate Alzheimer's disease.

**3. Galantamine (Reminyl)** starting dosage is 4 mg twice daily, taken with morning and evening meals. After four weeks, the dosage is increased to 8 mg twice daily. An increase to 12 mg twice daily may be considered. The most common side effects are nausea, vomiting, and diarrhea, which can be minimized by titrating the dosage gradually and taking the medication with meals. Improvement of cognitive and functional outcomes and behavioral symptoms has been demonstrated.

**4. Tacrine (Cognex)** is a second-line agent because, unlike the newer cholinesterase inhibitors, tacrine causes elevation of liver enzyme levels; thus, biweekly liver tests are necessary.

**5.**Beneficial response to a cholinesterase inhibitor can be determined from the physician's global assessment of the patient, the primary caregiver's report, a neuropsychologic assessment or mental status questionnaire, or evidence of behavioral or functional changes. Observation for six to 12 months is usually necessary to assess potential benefit.

**B.Vitamin E** intake of 2,000 IU daily of may slow the progression of functional symptoms.

**C.N-methyl-D-aspartate (NMDA) receptor antagonists**

**1.**Glutamate is the principle excitatory amino acid neurotransmitter in cortical and hippocampal neurons. One of the receptors activated by glutamate is the N-methyl-D-aspartate (NMDA) receptor, which is involved in learning and memory.

**2.Memantine** (**Axura, Ebixa**) is an NMDA receptor antagonist. In patients with mild-to-moderate vascular dementia (mini mental status examination scores 12 to 20), memantine significantly improves cognitive abilities. There were no serious side effects with therapy. This may represent a promising avenue for the treatment of vascular dementia.

**IV.Comorbid conditions.** Depression is common in older adults, including those with Alzheimer's disease. Selective serotonin reuptake inhibitors, such as citalopram (Celexa) and sertraline (Zoloft), appear to be effective and have few side effects; thus, they are the agents of choice for the treatment of depression.

**References:** See page 255.

# *Endocrinologic and Hematologic Disorders*

## Diabetes

Up to 4 percent of Americans have diabetes. Vascular disease accounts for over 70 percent of deaths in adults with diabetes.

**I.Classification and pathophysiology**

**A.Type 1 diabetes mellitus** primarily occurs in children and adolescents. Patients with type 1 diabetes have an absolute deficiency of endogenous insulin and require exogenous insulin for survival.

**B.Type 2 diabetes** accounts for 90% of individuals with diabetes mellitus, and the incidence increases in frequency with age, obesity and physical inactivity. The initial problem in type 2 diabetes is resistance to the action of insulin at the cellular level.

**II.Screening**

**A.**All adults should be screened for diabetes at regular intervals. Factors that confer an increased risk for development of diabetes include impaired glucose tolerance, hypertension, lipid disorders, coronary artery disease, obesity, and physical inactivity.

**B.**A fasting plasma glucose test is recommended for screening. A level of 110 to 125 mg/dL is considered "impaired fasting glucose," and a value of greater than or equal to 126 mg/dL, if confirmed on repeat testing, establishes the diagnosis of diabetes. If a patient is found to have a random plasma glucose level over 160 mg/dL, more formal testing with a fasting plasma glucose should be considered.

**Criteria for Diagnosis of Diabetes in Nonpregnant Adults**

Fasting plasma glucose 126 mg/dL or higher
**or**
Random plasma glucose 200 mg/dL or higher with symptoms of diabetes (fatigue, weight loss, polyuria, polyphagia, polydipsia)
**or**
Abnormal two-hour 75-g oral glucose tolerance test result, with glucose 200 mg/dL or higher at two hours
Any abnormal test result must be repeated on a subsequent occasion to establish the diagnosis

**III.Screening for microvascular complications in diabetics**

**A.Retinopathy.** Diabetic retinopathy and macular degeneration are the leading causes of blindness in diabetes. Adults with diabetes should receive annual dilated retinal examinations beginning at the time of diagnosis.

**B.Nephropathy.** Diabetes-related nephropathy affects 40% of patients with type 1 disease and 10-20% of those with type 2 disease. Microalbuminuria can be detected with annual urine screening for albumin/creatinine ratio.

**C.Peripheral neuropathy** affects many patients with diabetes and causes nocturnal or constant pain, tingling and numbness. The feet should be evaluated regularly for sensation, pulses and sores.

**D.Autonomic neuropathy** is found in many patients with long-standing diabetes, resulting in diarrhea, constipation, gastroparesis, vomiting, orthostatic hypotension, and erectile or ejaculatory dysfunction.

| Routine Diabetes Care |
|---|
| **History**<br>Review physical activity, diet, self-monitored blood glucose readings, medications<br>Assess for symptoms of coronary heart disease<br>Evaluate smoking status, latest eye examination results, foot care |
| **Physical examination**<br>Weight<br>Blood pressure<br>Foot examination<br>Pulse<br>Sores or callus<br>Monofilament test for sensation<br>Insulin injection sites<br>Refer for dilated retinal examination annually |
| **Laboratory studies**<br>HbA1c every three to six months<br>Annual fasting lipid panel<br>Annual urine albumin/creatinine ratio<br>Annual serum creatinine |

**IV.Treatment of type 2 diabetes mellitus**

**A.**The patient should monitor his fasting blood glucose. Some readings should also be obtained after meals and at other times during the day, and when hypoglycemia is suspected.

| American Diabetes Association goals for the treatment of diabetes | |
|---|---|
| Preprandial blood glucose level | 80 to 120 mg/dL |
| Bedtime blood glucose level | 100 to 140 mg/dL |
| Normal hemoglobin $A_{1c}$ ($HbA_{1c}$) level | 4% to 6% |
| Target $HbA_{1c}$ level | <7% |
| "Take action" $HbA_{1c}$ level | >8% |

**V.Sulfonylureas**

**A.**Sulfonylureas promote increased pancreatic insulin secretion. Sulfonylureas can lead to hypoglycemia and weight gain. All members of this drug class appear to be equally efficacious, with a decrease in fasting plasma glucose concentration of 60 to 70 mg/dL and a drop in $HbA_{1c}$ levels of about 1.5% to 2%.

**B.**Most patients who are of normal weight or only moderately obese should initially take a sulfonylurea. A typical initial sulfonylurea regimen consists of 2.5 mg of glipizide (Glucotrol) or glyburide (Micronase) taken before breakfast. If adequate glycemic control is not attained in the next two to four weeks, the dose can be increased to 5 mg and then 10 mg.

**VI.Meglitinides**

**A.**The mechanism of action of the meglitinides is similar to that of the sulfonylureas. Unlike sulfonylureas, however, meglitinides have a "quick on-quick off" action that offers improved postprandial control and reduces the incidence of late postprandial hypoglycemia.

**B.**The efficacy of the meglitinides is similar to that of the sulfonylureas, leading to a decrease in the fasting plasma glucose level of 60 mg/dL and in $HbA_{1c}$ of 1.7% to 1.9%. The main disadvantages of the meglitinides are their frequent dosing requirements and the risk for hypoglycemia and hyperinsulinemia, which is the same as with the sulfonylureas.

**C.Repaglinide (Prandin)** is taken shortly before each meal in doses ranging from 0.5 to 4 mg, up to three or four times a day. It may benefit patients with unpredictable meal schedules or large postprandial glucose excursions.

**D.Nateglinide (Starlix)** is a derivative of phenylalanine. Nateglinide appears to have a faster onset and disappearance of action than repaglinide but a somewhat reduced efficacy. 60-120 mg tid before meals.

**VII.Biguanides**

**A.Metformin (Glucophage)**, a biguanide, decreases hepatic glucose production. Gastrointestinal distress is common (eg, abdominal pain, nausea, diarrhea), most prominent during initiation of therapy. The incidence of lactic acidosis from metformin is only 0.03 per 1,000 patient-years.

**B.**Metformin lowers fasting plasma glucose levels by 60 to 70 mg/dL and $HbA_{1c}$ by 1.5% to 2.0%. It is equally efficacious in non-obese patients. It is an appropriate first-line therapy for patients of any weight.

**Contraindications to metformin therapy**

Renal dysfunction
- Serum creatinine level ≥1.5 mg/dL in men, ≥1.4 mg/dL in women
- Metformin should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials. Treatment may be restarted 48 hours after the procedure when normal renal function is documented.
- Treatment should be carefully initiated in patients ≥80 years of age after measurement of creatinine clearance demonstrates that renal function is not reduced.

Congestive heart failure that requires pharmacologic therapy
Hepatic dysfunction
Dehydration
Acute or chronic metabolic acidosis (diabetic ketoacidosis)
Known hypersensitivity to metformin

**VIII. Alpha-glucosidase inhibitors**

**A.** The alpha-glucosidase inhibitors slow the rate of absorption of carbohydrates. The use of acarbose (Precose) and miglitol (Glyset) is limited by both their relatively mild efficacy and the high frequency of gastrointestinal distress. These drugs may be suitable for mild diabetes or for those taking other oral agents who continue to have large postprandial blood glucose increases. They must be taken with each meal to reduce the rise of postprandial plasma glucose levels.

**B.** Alpha-glucosidase inhibitors decrease postprandial plasma glucose levels by 40 to 60 mg/dL, fasting plasma glucose levels by 20 to 30 mg/dL, and $HbA_{1c}$ levels by 0.5% to 1.0%. Many patients experience abdominal bloating, cramping, and flatulence during initial therapy.

**C. Acarbose (Precose)** is available as 50 and 100 mg tablets which should be taken with the first bite of each meal; 50 mg three times daily.

**D. Miglitol (Glyset)** may be started at 50 mg tid with the first bite of each meal.

**IX. Thiazolidinediones**

**A.** Thiazolidinediones increase insulin sensitivity in muscle resulting in lower circulating glucose concentrations. Thiazolidinediones, **rosiglitazone (Avandia) and pioglitazone (Actos)**, decrease fasting plasma glucose by 30 to 60 mg/dL and decrease $HbA_{1c}$ level by 1% to 1.5%. Pioglitazone is given once daily and rosiglitazone once or twice daily. Rosiglitazone and pioglitazone may be used for monotherapy or in combination with metformin or a sulfonylurea or insulin. Thiazolidinediones are no more effective than metformin, and they should be used only in patients who have contraindications to metformin.

**B.** Adverse effects of thiazolidinedione therapy include weight gain and peripheral edema. Expansion of the extracellular fluid space can occur, and anemia is occasionally seen. Therapy is contraindicated in advanced congestive heart failure.

**X. Choice of agent**

**A. Diet, weight loss, and exercise** remain the most important initial steps in the management of type 2 diabetes. Pharmacologic therapy is mandatory for patients who are unable to achieve glycemic control with lifestyle modifications or who have significant symptoms.

**B. Lean patients** with type 2 diabetes usually have insulin deficiency as the predominant feature, and a sulfonylurea is recommended in this subgroup. If control remains suboptimal, metformin or an alpha-glucosidase inhibitor may be added. First-line therapy with metformin is also reasonable, especially if glucose levels are only mildly elevated, because risk of hypoglycemia in these patients is increased with sulfonylurea therapy.

**C. Overweight patients.** Metformin should be considered the first-line agent because of the weight loss and lack of hypoglycemia. If control is suboptimal with metformin, the addition of a thiazolidinedione may be beneficial. If adequate control cannot be achieved with two drugs, the addition of a third oral agent should be considered. Alternatively, insulin could be added or substituted entirely (a patient who is 20 percent above ideal body weight and has a fasting blood glucose of 180 mg/dL should be started on a total dose of 21 units per day).

**Pharmacotherapy of Type 2 Diabetes**

| Agent | Starting dose | Maximum dose | Comments |
|---|---|---|---|
| **Sulfonylureas** | | | |
| Glipizide (Glucotrol) | 5 mg daily | 20 mg twice daily | May cause hypoglycemia, weight gain. Maximum dose should be used only in combination with insulin therapy |
| Glyburide (DiaBeta, Micronase) | 2.5 mg daily | 10 mg twice daily | |
| Glimepiride (Amaryl) | 1 mg daily | 8 mg daily | |
| **Biguanide** | | | |
| Metformin (Glucophage) | 500 mg daily | 850 mg three times daily | Do not use if serum creatinine is greater than 1.4 mg/dL in women or 1.5 mg/dL in men or in the presence of heart failure, chronic obstructive pulmonary disease or liver disease; may cause lactic acidosis |

| Agent | Starting dose | Maximum dose | Comments |
|---|---|---|---|
| **Glyburide/ metformin (Glucovance)** | 25 mg/250 mg; 2.5 mg/500 mg; 5 mg/500 mg | 1 tab qAM-bid | |
| **Thiazolidinediones**<br>Pioglitazone (Actos)<br>Rosiglitazone (Avandia) | 15 mg daily<br>4 mg daily | 45 mg per day<br>4 mg twice daily | Should be used only in patients who have contraindications to metformin |
| **Alpha-glucosidase inhibitor**<br>Acarbose (Precose)<br>Miglitol (Glyset) | 50 mg tid<br>50 mg tid | 100 mg three times daily<br>100 mg three times daily | Flatulence; start at low dose to minimize side effects; take at mealtimes |
| **Meglitamide**<br>Repaglinide (Prandin)<br>Nateglinide (Starlix) | 0.5 mg before meals<br>120 mg tid before meals or 60 mg tid before meals | 4 mg tid-qid<br>120 mg tid | Take at mealtimes |

## XI.Treatment of type 1 diabetes mellitus

| Goals of intensive diabetes treatment | | | |
|---|---|---|---|
| Premeal blood glucose level | Postprandial (ie, mealtime) glucose level | Bedtime glucose level | Hemoglobin $A_{1c}$ ($HbA_{1c}$) level |
| 90 to 130 mg/dL | 120 to 180 mg/dL | 110 to 150 mg/dL | Less than 6.5% |

### A.Basics of insulin use

**1.**Tighter control is recommended for pregnant women. Looser control may be appropriate in young children; elderly patients with active cardiac, cognitive, or visual disorders; and patients who (1) have hypoglycemic unawareness or recurrent severe hypoglycemia, (2) abuse alcohol or drugs, (3) have poor social support, or (4) have diabetes resulting from combined exocrine and endocrine pancreatic failure. Looser control is also indicated in patients in whom a hypoglycemic event might put them or others in danger (eg, bus drivers).

**2.Starting insulin dose** in otherwise healthy patients in whom type 1 diabetes was recently diagnosed, during the “honeymoon period” is typically 10 to 15 U/day (or 0.2 to 0.6 U/kg per day). Two-thirds of the total dose of intermediate-acting isophane insulin suspension (NPH, or N) is given in the morning and one-third at dinnertime. Short-acting regular insulin or a more rapid-acting insulin, such as lispro (LP) or aspart (as insulin analogue), is given with breakfast and dinner.

**3.**Over time, patients who have type 1 diabetes without intercurrent illness typically need 0.5 to 1 U/kg per day. Higher doses may be required during pregnancy and the adolescent growth spurt. If the patient's condition is unstable because of diabetic ketoacidosis, the insulin requirements may rise in the short term to 1 to 1.5 U/kg per day or higher.

| Initiating Insulin Therapy in a Patient with Newly Diagnosed Type 1 Diabetes |
|---|
| The total daily insulin dosage is 0.3 unit per kg of body weight.<br>Two-thirds of the total daily insulin dose may be given 20 to 30 minutes before breakfast and one-third of the dose may be given 20 to 30 minutes before the evening meal.<br>NPH insulin and regular insulin can be given in a 2:1 ratio for the breakfast dose and a 1:1 ratio for the evening-meal dose.<br>As more complete insulin deficiency develops this regimen becomes less effective. |

| Pharmacokinetic properties of types of insulin | | | | |
|---|---|---|---|---|
| **Type of insulin** | **Onset** | **Peak effect** | **Duration of action** | **Dosing interval** |
| **Mealtime Insulin** | | | | |
| Lispro (Humalog) (rapid-acting) | 5-15 min | 30 min-1.5 hr | 2 to 4 hours | Mealtime |

| Type of insulin | Onset | Peak effect | Duration of action | Dosing interval |
|---|---|---|---|---|
| Aspart (Novolog) (rapid-acting) | 5-15 min | 1-2 hr | | Mealtime |
| Regular (Humulin R) (short-acting) | 30-60 min | 2-4 hr | 5 to 8 hours | 20-45 min before meals |
| **Background Insulin** | | | | |
| Isophane insulin suspension (NPH) (Humulin N) (intermediate-acting) | 45 min-3 hr | 4.5-7 hr | 18 to 28 hours | Twice daily |
| Lente (Humulin L) (intermediate-acting) | 1-3 hr | 6-8 hr | 13 to 20 hours | Twice daily |
| Glargine (Lantus) (long-acting) | 1.5-2 hr | No peak | 13 to 18 hours | Once daily |

**4.**In patients with type 2 diabetes in whom oral agents have failed, the starting dose of N insulin is 0.15 U/kg at bedtime (when oral agents are continued) or a total multidose regimen of 0.3 to 0.7 U/kg per day (when all oral agents are discontinued). The total insulin dose required in obese patients with type 2 diabetes averages 1.2 U/kg per day.

**5.Lispro insulin** is superior to regular insulin in controlling postprandial glucose spikes when given in addition to a background insulin. Other advantages of lispro insulin are that it can be injected anytime from 15 minutes before to shortly after the meal, and it carries less risk of hypoglycemia and weight gain.

**6.Glargine** insulin is a human insulin that is slowly released, resulting in a relatively constant concentration over 24 hours with no pronounced peak. When patients are switched to glargine from twice-daily N insulin, it is suggested that 10% to 20% less glargine be given than the previous daily total dose of N insulin. Patients require regular, lispro, or aspart insulin boluses with each meal. Because of its consistency and prolonged action, glargine is a superior background insulin. Other peakless long-acting analogues (eg, Determir) will be available soon.

**B.Multiple-dose strategies**

**1.**Near-normoglycemia usually requires two to four daily injections or use of the insulin pump.

**2.**The most physiologic ratio of mealtime insulin to background insulin is 50:50. However, some active adolescents do best on a 60:40 ratio, whereas more sedentary adults might need a 40:60 ratio.

| Conventional and intensive insulin regimes | | | | | |
|---|---|---|---|---|---|
| **No. of injections** | **Regimen 8 AM/Noon/6 PM/10PM** | **Morning dose** | **Noon dose** | **Dinner dose** | **Bedtime dose** |
| **Two injections** | | | | | |
| 40% mealtime | N+R/0/N+R/0 or | 20% R or LP | - | 20% R or LP | - |
| 60% background | N+LP/0/N+LP/0 | 40% N | - | 20% N | - |
| Three injections | | | | | |
| 40% mealtime | N+LP/0/LP/N or | 20% LP or R | - | 20% LP or R | - |
| 60% background | N+R/0/R/N | 40% N | - | - | 20% N |
| **Three injections** | | | | | |
| 50% mealtime | U+R/R/U+R/0 or | 15% R or LP | 15% R or LP | 20% R or LP | - |
| 50% background | U+LP/LP/U+LP/0 | 20% U | - | 30% | - |

**References:** See page 255.

# Hypothyroidism

Hypothyroidism is second only to diabetes mellitus as the most common endocrine disorder, and its prevalence may be as high as 18 cases per 1,000 persons in the general population. The disorder becomes increasingly common with advancing age, affecting about 2 to 3 percent of older women.

## I. Etiology

### A. Primary hypothyroidism

**1.** The most common cause of hypothyroidism is Hashimoto's (chronic lymphocytic) thyroiditis. Most patients who have Hashimoto's thyroiditis have symmetrical thyroid enlargement, although many older patients with the disease have atrophy of the gland. Anti-thyroid peroxidase (TPO) antibodies are present in almost all patients. Some patients have blocking antibodies to the thyroid-stimulating hormone (TSH) receptor.

**2.** Hypothyroidism also occurs after treatment of hyperthyroidism by either surgical removal or radioiodine ablation. Less common causes of hypothyroidism include congenital dyshormonogenesis, external radiotherapy, infiltrative diseases, such as amyloidosis, and peripheral resistance to thyroid hormone action.

**B. Secondary and central hypothyroidism.** Pituitary and hypothalamic dysfunction can lead to hypothyroidism. Pituitary adenomas, craniopharyngiomas, pinealomas, sarcoidosis, histiocytosis X, metastatic disease, primary central nervous system (CNS) neoplasms (eg, meningioma), and head trauma all may cause hypothyroidism.

**C. Transient hypothyroidism.** Subacute thyroiditis is frequently associated with a hyperthyroid phase of 4 to 12 weeks' duration; a 2- to 16-week hypothyroid phase follows, before recovery of thyroid function. Subacute granulomatous (de Quervain's) thyroiditis and subacute lymphocytic (painless) thyroiditis are viral and autoimmune disorders, respectively; the latter condition may occur post partum.

## II. Diagnosis

**A. Symptoms and signs** of hypothyroidism include fatigue, weight gain, muscle weakness and cramps, fluid retention, constipation, and neuropathy (eg, carpal tunnel syndrome). Severe hypothyroidism may be associated with carotenemia, loss of the lateral aspect of the eyebrows, sleep apnea, hypoventilation, bradycardia, pericardial effusion, anemia, hyponatremia, hyperprolactinemia, hypercholesterolemia, hypothermia, and coma.

**B.** In patients with primary hypothyroidism, the thyroid-stimulating hormone (TSH) level is elevated, and free thyroid hormone levels are depressed. In contrast, patients with secondary hypothyroidism have a low or undetectable TSH level.

**C.** TSH results have to be interpreted in light of the patient's clinical condition. A low TSH level should not be misinterpreted as hyperthyroidism in the patient with clinical manifestations of hypothyroidism. When symptoms are nonspecific, a follow-up assessment of the free thyroxine ($T_4$) level can help distinguish between primary and secondary hypothyroidism.

**Laboratory Values in Hypothyroidism**

| TSH level | Free $T_4$ level | Free $T_3$ level | Likely diagnosis |
|---|---|---|---|
| High | Low | Low | Primary hypothyroidism |
| High (>10 μU per mL) | Normal | Normal | Subclinical hypothyroidism with high risk for future development of overt hypothyroidism |
| High (6 to 10 μU per mL) | Normal | Normal | Subclinical hypothyroidism with low risk for future development of overt hypothyroidism |
| High | High | Low | Congenital absence of $T_4$-$T_3$–converting enzyme; amiodarone (Cordarone) effect on $T_4$-$T_3$ conversion |
| High | High | High | Peripheral thyroid hormone resistance |
| Low | Low | Low | Pituitary thyroid deficiency or recent withdrawal of thyroxine after excessive replacement therapy |

| Causes of Hypothyroidism |
|---|
| **Primary hypothyroidism (95% of cases)**<br>Idiopathic hypothyroidism<br>Hashimoto's thyroiditis Irradiation of the thyroid subsequent to Graves' disease<br>Surgical removal of the thyroid<br>Late-stage invasive fibrous thyroiditis<br>Iodine deficiency<br>Drug therapy (eg, lithium, interferon)<br>Infiltrative diseases (eg, sarcoidosis, amyloidosis, scleroderma, hemochromatosis) |
| **Secondary hypothyroidism (5% of cases)**<br>Pituitary or hypothalamic neoplasms<br>Congenital hypopituitarism<br>Pituitary necrosis (Sheehan's syndrome) |

## III. Treatment of hypothyroidism

### A. Initiating thyroid hormone replacement

**1.** Most otherwise healthy adult patients with hypothyroidism require thyroid hormone replacement in a dosage of 1.7 mcg per kg per day, with requirements falling to 1 mcg per kg per day in the elderly. Thus, (Synthroid) in a dosage of 0.10 to 0.15 mg per day is needed to achieve euthyroid status. For full replacement, children may require up to 4 mcg per kg per day.

**2.** In young patients without risk factors for cardiovascular disease, thyroid hormone replacement can start close to the target goal. In most healthy young adults, replacement is initiated using levothyroxine in a dosage of 0.075 mg per day, with the dosage increased slowly as indicated by continued elevation of the TSH level.

**3.** Levothyroxine (Synthroid) should be initiated in a low dosage in older patients and those at risk for cardiovascular compromise; the usual starting dosage is 0.025 mg per day, increased in increments of 0.025 to 0.050 mg every four to six weeks until the TSH level returns to normal.

**Commonly Prescribed Thyroid Hormone Preparations**

| Generic Name | Brand Name(s) | Approximate Equivalent Dose | Preparations |
|---|---|---|---|
| Levothyroxine | Synthroid<br>Levothroid<br>Levoxyl<br>Eltroxin | 100 mcg | Tablets: 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, 300 mcg |

## IV. Monitoring thyroid function

**A.** In patients with an intact hypothalamic-pituitary axis, the adequacy of thyroid hormone replacement can be followed with serial TSH assessments. The TSH level should be evaluated no earlier than four weeks after an adjustment in the levothyroxine dosage. The full effects of thyroid hormone replacement on the TSH level may not become apparent until after eight weeks of therapy.

**B.** In patients with pituitary insufficiency, measurements of free $T_4$ and $T_3$ levels can be performed to determine whether patients remain euthyroid. TSH or free $T_4$ levels are monitored annually in most patients with hypothyroidism.

## V. Subclinical Hypothyroidism

**A.** The TSH level can be mildly elevated when the free $T_4$ and $T_3$ levels are normal, a situation that occurs most often in women and becomes increasingly common with advancing age. This condition has been termed "subclinical hypothyroidism."

**B.** In patients at higher risk for osteoporosis or fractures, the deleterious effects of excessive thyroid hormone can be avoided by withholding replacement until the free $T_4$ and $T_3$ levels drop below normal.

**References:** See page 255.

# Thyroiditis

Thyroiditis refers to a group of inflammatory diseases affecting the thyroid gland.

| Classification of Thyroiditis | |
|---|---|
| **Histologic classification** | **Synonyms** |
| Chronic lymphocytic | Chronic lymphocytic thyroiditis, Hashimoto's thyroiditis |
| Subacute lymphocytic | Subacute lymphocytic thyroiditis: (1) postpartum thyroiditis and (2) sporadic painless thyroiditis |
| Granulomatous | Subacute granulomatous thyroiditis, de Quervain's thyroiditis |
| Microbial inflammatory | Suppurative thyroiditis, acute thyroiditis |
| Invasive fibrous | Riedel's struma, Riedel's thyroiditis |

**I.Chronic Lymphocytic Thyroiditis (Hashimoto's Thyroiditis)**

**A.**Chronic lymphocytic thyroiditis is the most common inflammatory condition of the thyroid gland and the most common cause of goiter. It is an autoimmune condition.

**B.**Chronic lymphocytic thyroiditis is the most common cause of hypothyroidism, and euthyroid persons with Hashimoto's disease develop hypothyroidism at a rate of 5 percent per year. Up to 95 percent of cases of chronic lymphocytic thyroiditis occur in women, usually between 30 and 50 years of age.

**C.Clinical Manifestations**. Hashimoto's thyroiditis is usually asymptomatic. Symptoms of hypothyroidism are present in 20 percent of patients. Physical examination generally reveals a firm, irregular, nontender goiter. The definitive indicator of chronic lymphocytic thyroiditis is the presence of thyroid-specific autoantibodies in the serum. A dominant nodule in a patient with Hashimoto's disease should prompt a fine-needle aspiration biopsy to exclude malignancy.

**D.Treatment**. Because thyroiditis is usually asymptomatic, many patients do not require treatment. When hypothyroidism is present, treatment with thyroxine (T4) is indicated. Lifetime replacement of levothyroxine is indicated in hypothyroid patients, at a starting dosage of 25 to 50 µg per day, with gradual titration to an average daily dosage of 75 to 150 µg.

**II.Subacute Lymphocytic Thyroiditis**

**A.**Subacute lymphocytic thyroiditis occurs most often in the postpartum period but may also occur sporadically. Antimicrosomal antibodies are present in 50 to 80 percent of patients, while antithyroid peroxidase antibodies are present in nearly all patients. Subacute lymphocytic thyroiditis starts with an initial hyperthyroid phase, followed by subsequent hypothyroidism and, finally, a return to the euthyroid state. In the postpartum patient, thyrotoxicosis usually develops in the first three months following delivery and lasts for one or two months.

**B.**Patients usually present with tachycardia, palpitations, heat intolerance, nervousness and weight loss. A small painless goiter is present in 50 percent. T4 and triiodothyronine (T3) levels are initially elevated.

**C.Treatment**. Acute symptoms of hyperthyroidism are managed with beta blockers. Antithyroid drugs are not indicated. Replacement of thyroid hormone in the hypothyroid phase is indicated if the patient's symptoms are severe. If the hypothyroid phase lasts longer than six months, permanent hypothyroidism is likely.

**III.Subacute Granulomatous Thyroiditis**

**A.**Subacute granulomatous thyroiditis is the most common cause of a painful thyroid gland. It is most likely caused by a viral infection and is generally preceded by an upper respiratory tract infection.

**B.Clinical Manifestations**

**1.**Subacute granulomatous thyroiditis presents with acute onset of pain in the thyroid. Symptoms of hypermetabolism may be present, and the ESR usually is markedly elevated. A normal ESR essentially rules out the diagnosis of subacute granulomatous thyroiditis. The thyroid is firm, nodular and tender. Thyrotoxicosis is present in 50 percent of patients. Serum TSH concentrations are low.

**2.Clinical Management**

**a.**The acute phase of thyroid pain and thyrotoxicosis may last three to six weeks. Hypothyroidism often ensues and may last weeks to months or may be permanent (in up to 5 percent of patients).

**b.**Therapy with antithyroid drugs is not indicated. Therapy with beta blockers may be indicated for the symptomatic treatment of thyrotoxicosis. Nonsteroidal anti-inflammatory drugs are generally effective in reducing mild thyroid pain in patients with mild cases. More severe disease requires a tapering dosage of prednisone (20 to 40 mg per day) given over two to four weeks.

**References:** See page 255.

# Thyrotoxicosis

**I.Diagnosis**

**A.**Thyrotoxicosis is characterized by heat intolerance, weight loss or gain, palpitations, anxiety, tachycardia, and

tremor with elevated levels of the thyroid hormones thyroxine ($T_4$) and triiodothyronine ($T_3$). Hyperthyroidism refers to the more common forms of thyrotoxicosis in which there is overproduction of thyroid hormones, usually due to stimulation of the thyroid by thyroid-stimulating hormone (TSH) receptor autoantibodies (Graves' disease) or toxic multinodular goiter and toxic adenoma.

**B.**Thyrotoxicosis is confirmed by a low-serum TSH concentration, usually in association with elevations of the serum free $T_4$ or $T_3$ concentrations. Mild thyrotoxicosis, sometimes termed "subclinical thyrotoxicosis," is characterized by suppression of TSH levels in association with high-normal serum $T_4$ and $T_3$ concentrations. Rare conditions causing TSH-mediated hyperthyroidism (ie, TSH-secreting pituitary tumors) are typically associated with elevated-free $T_4$ and $T_3$ concentrations with an elevated or inappropriately normal TSH level. Isolated suppression of TSH can also be seen in patients with severe nonthyroidal illnesses. Consequently, it is usually necessary to measure the serum TSH and free $T_4$ concentrations to confirm or exclude thyrotoxicosis with absolute certainty.

**C.**True hyperthyroidism can be distinguished from other causes with a nuclear thyroid scan. An increased glandular concentration of tracer indicates that hyperthyroidism is present. In contrast, decreased tracer uptake is typically present with inflammatory disorders (eg, subacute [de Quervain's], lymphocytic [postpartum, silent, painless], or suppurative thyroiditis) with exogenous thyroid hormones.

**D.**TSH receptor-stimulating and -binding immunoglobulins are usually detectable in Graves' disease. The erythrocyte sedimentation rate is typically elevated in subacute thyroiditis. Circulating human chorionic gonadotropin is detectable in choriocarcinoma and molar pregnancy.

**II.Treatment**

**A.Beta-Adrenergic Blocking Agents**

**1.**Beta-adrenergic blocking agents (beta-blockers) are used to control tremor, palpitations, anxiety, and insomnia. Propranolol (Inderal) offers the advantage of partially inhibiting the peripheral conversion of $T_4$ to $T_3$.

**Drugs Used in the Treatment of Hyperthyroidism**

| Agent | Name | Available Doses | Usual Starting Dose |
|---|---|---|---|
| **Beta-blockers** | | | |
| Propranolol<br>Regular<br><br>Sustained-release | Inderal<br><br>Inderal LA | 10, 20, 40, 60, 80, 90 mg<br><br>60, 80, 120, 160 mg | 10-20 mg PO tid*<br><br>60-80 mg PO qd |
| Atenolol | Tenormin | 25, 50, 100 mg | 25-50 mg PO qd |
| Metoprolol<br>Regular<br>Extended-release | Lopressor<br>Toprol XL | 50, 100 mg<br><br>50, 100, 200 mg | 25-50 mg PO bid<br>50-100 mg qd |
| **Thioamides** | | | |
| Methimazole | Tapazole | 5, 10 mg | 20-40 mg PO qd |
| Propylthiouracil | PTU | 50 mg | 50-100 mg PO tid |
| **Iodine** | | | |
| Saturated solution of potassium iodide | SSKI | 50 mg/drop | 10 drops PO bid |

**2.Thioamide Antithyroid Drugs**

**a.**The thionamide antithyroid drugs are used to treat hyperthyroidism due to Graves' disease and toxic multinodular goiter. Methimazole (Tapazole) can be given on a once-daily dosing schedule. Propylthiouracil PTU, which must be taken more frequently, partially inhibits the peripheral conversion of $T_4$ to $T_3$, an effect that may be valuable in patients with severe thyrotoxicosis.

**b.**When PTU is used, it can be started at a dose of 50 to 100 mg every 6 to 8 hours. In patients with more severe hyperthyroidism, methimazole, 20 mg three times daily or 30 mg twice daily or PTU 100 to 200 mg every 6 hours, can be used.

**c.**Early in the course of treatment, the serum total or free $T_4$ and $T_3$ levels can be monitored at 2- to 4-week intervals. TSH becomes a useful parameter later in the course of treatment. Typically, the antithyroid drug dosage can be decreased once hyperthyroidism is controlled.

**d.**For patients with Graves' disease, a 9- to 12-month course of therapy is appropriate for most adults before tapering the agent off to determine whether TSH-receptor stimulatory activity has subsided. For patients with toxic adenomas and toxic multinodular goiter, antithyroid medication is strictly a temporary measure until radioiodine treatment or surgery is employed.

**e.**Fever, rash, and pruritus occur in approximately 5% of treated patients. Agranulocytosis occurs in approximately 2 of 1000 thionamide treated patients. PTU-associated hepatotoxicity is rare but can progress to acute hepatic failure and death. Methimazole-associated hepatotoxicity is usually

milder. Hematologic and liver function test should be monitored.

**3.Radioactive Iodine.** Radiation therapy with radioisotopes of iodine treatment is appropriate for the definitive treatment of Graves' disease, toxic adenoma, toxic multinodular goiter, and TSH-secreting pituitary adenomas. The principal side effect is hypothyroidism, which occurs in the majority of cured patients, necessitating lifelong follow-up.

**4.**Iodine in the form of a saturated solution of potassium iodide or Lugol's solution blocks the release of hormone from the gland and can be used (1) as short-term therapy to prepare patients for surgery, (2) as an adjunct to accelerate recovery after radioiodine treatment, or (3) as one component of polypharmacy for patients in thyrotoxic crisis. Aspirin, nonsteroidal anti-inflammatory agents, and glucocorticoids can be used to relieve pain.

**5.**Surgery is an appropriate treatment for hyperthyroidism in patients with toxic adenomas or toxic multinodular goiters who are younger than 20 years or whose glands are large enough to cause local symptoms or a cosmetic problem.

**B.Specific Conditions**

**1.Graves' Disease**

**a.**In patient with mild Graves' disease and thyrotoxicosis, there is a 30 to 40% probability of remission after a course of antithyroid drug therapy. Treatment is usually started with methimazole, which is then adjusted in increments of 5 to 10 mg per dose and continued until the free $T_4$ and $T_3$ levels return to normal. The minimal dose required to maintain euthyroidism is continued for 9 months to 1 year. Treatment is then tapered off to determine if hyperthyroidism recurs. If it does, patients should proceed with treatment with radioactive iodine.

**b.**Graves' disease appearing with moderate thyrotoxicosis and no significant complications is usually treated with radioactive iodine. However, many patients do not desire a permanent therapy and may request antithyroid medication.

**2.Toxic Multinodular Goiter and Toxic Adenoma.** For hyperthyroidism due to toxic multinodular goiter, radioactive iodine is generally the treatment of choice, although occasional surgery should be considered for cosmesis or relief of compressive symptoms. Patients younger than 20 years of age with a toxic adenoma should undergo surgery. In older patients, radioactive iodine may be used.

**C.Special Circumstances**

**1.Mild (Subclinical) Thyrotoxicosis** is diagnosed when the serum TSH concentration is very low or undetectable without elevations of the serum $T_4$ or $T_3$ concentrations. These patient may have no symptoms or signs of thyrotoxicosis. For individuals with nonspecific symptoms, a 3-month trial of antithyroid drug therapy may be useful.

**2.Thyrotoxic crisis or storm** is characterized by marked sympathomimetic and hypermetabolic effects of thyroid hormone excess. It typically develops in the setting of Graves' disease. Patients may develop high fever, atrial tachyarrhythmias, congestive heart failure, nausea and vomiting, diarrhea, delirium, psychosis, or

seizures. Therapy includes antipyretics, beta blockers, high-dose PTU, iodinated contrast agents, and glucocorticoids.

**References:** See page 255.

## Obesity

Obesity is a risk factor for many medical illnesses, and a modest reduction of 5% to 10% of body weight can modify risk factors for heart disease, including lipid levels, glycemic control, and blood pressure. Obesity is defined as a body mass index (BMI) of 30 kg per $m^2$ or more. Overweight is defined as a BMI of 25 to 29.9 kg per $m^2$.

**I.Diagnosis of obesity** begins with the determination of BMI. The BMI can be ascertained by measuring the patient's height and weight and then using a BMI table to find the BMI value. The distribution of fat based on the waist circumference or the waist-to-hip circumference ratio (WHR) and investigations for comorbid conditions such as diabetes mellitus, dyslipidemia, hypertension, and heart disease should be determined.

**II.Management**

**A.**For most patients, the initial weight loss objective should be a 10 percent reduction from baseline body weight over a period of about four to six months. After six months, the rate of weight loss often stabilizes or slows.

**B.**An overweight individual with a BMI of less than 30 kg per $m^2$ and no health risk factors should have a target, six-month BMI in the range of 20 to 27. A decrease of 300 to 500 kcal per day will produce weight losses of 0.5 to 1 lb per week (10 percent reduction at six months).

**C.Nutrition therapy**

**1.**A meal plan that creates an energy deficit of 500 to 1,000 kcal per day less than the individual's average daily intake will usually be suitable for weight reduction. Along with caloric reduction, a reduction in total fat consumption should be recommended. Caloric restrictions for the treatment of overweight and obesity can be classified as follows:

**a.**Moderate deficit diet (all health risk groups). Women: 1200+ kcal per day; men: 1400+ kcal per day

**b.**Low-calorie diet (moderate to extremely high health risk groups). Women: 800 to 1200 kcal per day; men: 800 to 1400+ kcal per day

**c.**Very low-calorie diet (high to extremely high-health risk groups). Less than 800 kcal per day.

**2.**Among patients treated with a moderate deficit diet, weight losses average about 1 lb (0.45 kg) per week.

**D.Physical activity.** Although most weight loss is achieved through decreased caloric intake, physical activity is the primary factor responsible for increased caloric expenditure. The long-term physical activity goal of most adults should be to perform 30 or more minutes of physical activity each day.

**III.Treatment of obesity**

**A.**Obesity is a chronic condition requiring long-term therapy. If obesity is not treated for the duration of the patient's life, obesity re-emerges as a potent comorbid risk factor for disability or premature death.

**B.**Candidates for use of weight loss drugs are patients who have failed to lose weight with diet and exercise therapy, have a body mass index greater than 27 to 30, or have risk factors or medical conditions caused by obesity. Weight loss medications should not be used by pregnant or lactating women. Any medical condition (eg, cardiovascular disease) should be stable before these drugs are prescribed. Anorexiants are contraindicated in patients with glaucoma**.**

**C.Goals of therapy.** Weight loss should exceed 2 kg during the first month of drug therapy, fall more than 5 percent below baseline by three to six months, and remain at this level to be considered effective. Weight loss of 10 to 15 percent is considered a good response and loss exceeding 15 percent is considered an excellent response. Weight loss may lower blood pressure and serum lipid concentrations, increase insulin sensitivity, and reduce hyperglycemia.

**Anorectic Medication for Obesity Treatment**

| Medication | Schedule | Trade Name(s) | Dosage (mg) | Common Use |
|---|---|---|---|---|
| Phentermine | IV | | 8, 15, 30 | Initial dose: 8-15 mg/d<br>Higher dose: 15 mg bid or 30 mg q AM |
| | | Adipex-P | 37.5 | Initial dose: 1/2 tablet/d<br>Higher dose: 1/2 tablet bid or 37.5-mg tablet q AM |
| | | Fastin | 30 | 1 capsule q AM |
| Phentermine resin | IV | Ionamin | 15, 30 | Initial dose: 15 mg/d<br>Higher dose: 15 mg bid or 30 mg q AM |

| Medication | Schedule | Trade Name(s) | Dosage (mg) | Common Use |
|---|---|---|---|---|
| Diethylpropion | IV | Tenuate<br>Tenuate Dospan (sustained-release form) | 25<br>75 | 25 mg tid<br>75 mg qd |
| Sibutramine | IV | Meridia | 5, 10, 15 | Initial dose: 5-10 mg/d<br>Higher dose: 15-25 mg/d |
| Orlistat | IV | Xenical | 120 | Initial dose: 1 capsule with a fatty meal qd; bid; or tid |

**D.Anorexiant therapy**

**1.**Anorexiants that have low potential for abuse are phentermine (eg, Adipex-P, Fastin, Ionamin), mazindol (Mazanor, Sanorex), and diethylpropion (Tenuate).

**2.**Anorexiants may cause patients to feel nervous or experience insomnia and dry mouth. Patients should expect to lose about 0.5 lb per week.

**E.Orlistat (Xenical) therapy**

**1.**Orlistat inhibits gastrointestinal lipases. Minor gastrointestinal side effects of steatorrhea, oily spotting, and fecal urgency usually resolve with continued use. One-fourth to one-half of motivated patients have success with orlistat therapy in that it prevents weight regain after dieting or it decreases weight by 5% to 10%.

**2.**Orlistat should be prescribed as 120 mg three times daily with meals, along with a diet restricted to 30% of calories obtained from fat. A multivitamin should be taken daily.

**F.Sibutramine (Meridia, Reductil) therapy**

**1.**Sibutramine is a serotonin and norepinephrine-uptake inhibitor that increases energy expenditure and satiety. Treatment with 10 to 15 mg/day of sibutramine results in weight loss between 10.6 to 13.4 lb. Sibutramine also has been shown to maintain weight loss attained by dieting.

**2.**Side effects include insomnia, dizziness, constipation, and dry mouth. Sibutramine increases heart rate 4 or 5 beats per minute and blood pressure by 1 to 3 mm Hg. Pre-existing hypertension should be controlled before sibutramine is prescribed.

**G.Metformin (Glucophage)** has been used for weight loss in patients who are overweight without diabetes. Women who combine metformin with a low-calorie and reduced carbohydrate diet can lose 20 to 30 pounds in one year. Metformin helps maintain weight loss. Initial dose is 500 mg BID with meals, increasing to 1500 mg/day.

**IV.Surgical therapy**

**A.**Surgical therapy should be considered in patients with severe obesity meeting the following criteria:

**1.**A BMI of 40 kg per $m^2$ or more and have failed in attempts at medical treatment, or

**2.**A BMI of 35 kg per $m^2$ or more with coexisting morbidities or other complicating risk factors.

**References:** See page 255.

# Hematologic and Rheumatologic Disorders

## Anemia

The prevalence of anemia is about 29 to 30 cases per 1,000 females of all ages and six cases per 1,000 males under the age of 45 Deficiencies of iron, vitamin B12 and folic acid are the most common causes.

**I.Clinical manifestations.** Severe anemia may be tolerated well if it develops gradually. Patients with an Hb of less than 7 g/dL will have symptoms of tissue hypoxia (fatigue, headache, dyspnea, light-headedness, angina). Pallor, syncope and tachycardia may signal hypovolemia and impending shock.

**II.History and physical examination**

**A.**The evaluation should determine if the anemia is of acute or chronic onset, and clues to any underlying systemic process should be sought. A history of drug exposure, blood loss, or a family history of anemia should be sought.

**B.**Lymphadenopathy, hepatic or splenic enlargement, jaundice, bone tenderness, neurologic symptoms or blood in the feces should be sought.

**III.Laboratory evaluation**

**A.Hemoglobin and hematocrit** serve as an estimate of the RBC mass.

**B.Reticulocyte count** reflects the rate of marrow production of RBCs. Absolute reticulocyte count = (% reticulocytes/100) × RBC count. An increase of reticulocytes to greater than 100,000/$mm^3$ suggests a hyperproliferative bone marrow.

**C.Mean corpuscular volume (MCV)** is used in classifying anemia as microcytic, normocytic or macrocytic.

**Normal Hematologic Values**

| Age of patient | Hemoglobin | Hematocrit (%) | Mean corpuscular volume ($pm^3$) |
|---|---|---|---|
| One to three days | 14.5-22.5 g per dL | 45-67 | 95-121 |
| Six months to two years | 10.5-13.5 g per dL | 33-39 | 70-86 |
| 12 to 18 years (male) | 13.0-16.0 g per dL | 37-49 | 78-98 |
| 12 to 18 years (female) | 12.0-16.0 g per dL | 36-46 | 78-102 |
| >18 years (male) | 13.5-17.5 g per dL | 41-53 | 78-98 |
| >18 years (female) | 12.0-16.0 g per dL | 36-46 | 78-98 |

**IV.Iron deficiency anemia**

**A.**Iron deficiency is the most common cause of anemia. In children, the deficiency is typically caused by diet. In adults, the cause should be considered to be a result of chronic blood loss until a definitive diagnosis is established.

**B.Laboratory results**

**1.**The MCV is normal in early iron deficiency. As the hematocrit falls below 30%, hypochromic microcytic cells appear, followed by a decrease in the MCV.

**2.A serum ferritin level** of less than 10 ng/mL in women or 20 ng/mL in men is indicative of low iron stores. A serum ferritin level of more than 200 ng/mL indicates adequate iron stores.

**C.Treatment of iron deficiency anemia**

**1.**Ferrous salts of iron are absorbed much more readily and are preferred. Commonly available oral preparations include ferrous sulfate, ferrous gluconate and ferrous fumarate (Hemocyte). All three forms are well absorbed. Ferrous sulfate is the least expensive and most commonly used oral iron supplement.

| Oral Iron Preparations | | | |
|---|---|---|---|
| **Preparation** | **Elemental iron (%)** | **Typical dosage** | **Elemental iron per dose** |
| Ferrous sulfate | 20 | 325 mg three times daily | 65 mg |
| Ferrous sulfate, exsiccated (Feosol) | 30 | 200 mg three times daily | 65 mg |
| Ferrous gluconate | 12 | 325 mg three times daily | 36 mg |
| Ferrous fumarate (Hemocyte) | 33 | 325 mg twice daily | 106 mg |

**2.**For iron replacement therapy, a dosage equivalent to 150 to 200 mg of elemental iron per day is recommended.

**3.**Ferrous sulfate, 325 mg of three times a day, will provide the necessary elemental iron for replacement therapy. Hematocrit levels should show improvement within one to two months.

**4.**Depending on the cause and severity of the anemia, replacement of low iron stores usually requires four to six months of iron supplementation. A daily dosage of 325 mg of ferrous sulfate is necessary for maintenance therapy.

**5.Side effects** from oral iron replacement therapy are common and include nausea, constipation, diarrhea and abdominal pain. Iron supplements should be taken with food; however, this may decrease iron absorption by 40 to 66 percent. Changing to a different iron salt or to a controlled-release preparation may also reduce side effects.

**6.**For optimum delivery, oral iron supplements must dissolve rapidly in the stomach so that the iron can be absorbed in the duodenum and upper jejunum. Enteric-coated preparations are ineffective since they do not dissolve in the stomach.

**7.**Causes of resistance to iron therapy include continuing blood loss, ineffective intake and ineffective absorption. Continuing blood loss may be overt (eg, menstruation, hemorrhoids) or occult (e.g., gastrointestinal malignancies, intestinal parasites, nonsteroidal anti-inflammatory drugs).

**V.Vitamin B12 deficiency anemia**

**A.**Since body stores of vitamin B12 are adequate for up to five years, deficiency is generally the result of failure to absorb it. Pernicious anemia, Crohn's disease and other intestinal disorders are the most frequent causes of vitamin B12 deficiency.

**B.**Symptoms are attributable primarily to anemia, although glossitis, jaundice, and splenomegaly may be present. Vitamin B12 deficiency may cause decreased vibratory and positional sense, ataxia, paresthesias, confusion, and dementia. Neurologic complications may occur in the absence of anemia and may not resolve completely despite adequate treatment. Folic acid deficiency does not cause neurologic disease.

**C. Laboratory results**

**1.**A macrocytic anemia usually is present, and leukopenia and thrombocytopenia may occur. Lactate dehydrogenase (LDH) and indirect bilirubin typically are elevated.

**2.**Vitamin B12 levels are low. RBC folate levels should be measured to exclude folate deficiency.

**D.Treatment of vitamin B12 deficiency anemia**. Intramuscular, oral or intranasal preparations are available for B12 replacement. In patients with severe vitamin B12 deficiency, daily IM injections of 1,000 mcg of cyanocobalamin are recommended for five days, followed by weekly injections for four weeks. Hematologic improvement should begin within five to seven days, and the deficiency should resolve after three to four weeks.

| Vitamin B12 and Folic Acid Preparations | |
|---|---|
| **Preparation** | **Dosage** |
| Cyanocobalamin tablets | 1,000 µg daily |
| Cyanocobalamin injection | 1,000 µg weekly |
| Cyanocobalamin nasal gel (Nascobal) | 500 µg weekly |
| Folic acid (Folvite) | 1 mg daily |

**VI.Folate deficiency anemia**

**A.**Folate deficiency is characterized by megaloblastic anemia and low serum folate levels. Most patients with folate deficiency have inadequate intake. Lactate dehydrogenase (LDH) and indirect bilirubin typically are elevated, reflecting ineffective erythropoiesis and premature destruction of RBCs.

**B.RBC folate and serum vitamin $B_{12}$ levels** should be measured. RBC folate is a more accurate indicator of body folate stores than is serum folate, particularly if measured after folate therapy has been initiated.

**C.Treatment of folate deficiency anemia**

**1.**A once-daily dosage of 1 mg of folic acid given PO will replenish body stores in about three weeks.

**2.**Folate supplementation is also recommended for women of child-bearing age to reduce the incidence of fetal neural tube defects. Folic acid should be initiated at 0.4 mg daily before conception. Prenatal vitamins contain this amount. Women who have previously given birth to a child with a neural tube defect should take 4 to 5 mg of folic acid daily.

**References:** See page 255.

# Low Back Pain

Approximately 90 percent of adults experience back pain at some time in life, and 50 percent of persons in the working population have back pain every year.

**I.Evaluation of low back pain**

**A.**A comprehensive history and physical examination can identify the small percentage of patients with serious conditions such as infection, malignancy, rheumatologic diseases and neurologic disorders.

**B.**The history and review of systems include patient age, constitutional symptoms and the presence of night pain, bone pain or morning stiffness. The patient should be asked about the occurrence of visceral pain, claudication, numbness, weakness, radiating pain, and bowel and bladder dysfunction.

**History and Physical Examination in the Patient with Acute Low Back Pain**

**History**
Onset of pain (eg, time of day, activity)
Location of pain (eg, specific site, radiation of pain)
Type and character of pain (sharp, dull)
Aggravating and relieving factors
Medical history, including previous injuries
Psychosocial stressors at home or work
"Red flags": age greater than 50 years, fever, weight loss
Incontinence, constipation
**Physical examination**
Informal observation (eg, patient's posture, expressions, pain behavior)
Physical examination, with attention to specific areas as indicated by the history
Neurologic evaluation
Back examination
- Palpation
- Range of motion or painful arc
- Stance
- Gait
- Mobility (test by having the patient sit, lie down and stand up)
- Straight leg raise test

**C.**Specific characteristics and severity of the pain, a history of trauma, previous therapy and its efficacy, and the functional impact of the pain on the patient's work and activities of daily living should be assessed.

**D.**The most common levels for a herniated disc are L4-5 and L5-S1. The onset of symptoms is characterized by a sharp, burning, stabbing pain radiating down the posterior or lateral aspect of the leg, to below the knee. Pain is generally superficial and localized, and is often associated with numbness or tingling. In more advanced cases, motor deficit, diminished reflexes or weakness may occur.

**E.If a disc herniation** is responsible for the back pain, the patient can usually recall the time of onset and contributing factors, whereas if the pain is of a gradual onset, other degenerative diseases are more probable than disc herniation.

**F.**Rheumatoid arthritis often begins in the appendicular skeleton before progressing to the spine. Inflammatory arthritides, such as ankylosing spondylitis, cause generalized pain and stiffness that are worse in the morning and relieved somewhat throughout the day.

**G.Cauda equina syndrome.** Only the relatively uncommon central disc herniation provokes low back pain and saddle pain in the S1 and S2 distributions. A central herniated disc may also compress nerve roots of the cauda equina, resulting in difficult urination, incontinence or impotence. If bowel or bladder dysfunction is present, immediate referral to a specialist is required for emergency surgery to prevent permanent loss of function.

**II.Physical and neurologic examination of the lumbar spine**

**A.External manifestations of pain**, including an abnormal stance, should be noted. The patient's posture and gait should be examined for sciatic list, which is indicative of disc herniation. The spinous processes and interspinous ligaments should be palpated for tenderness.

**B.Range of motion** should be evaluated. Pain during lumbar flexion suggests discogenic pain, while pain on lumbar extension suggests facet disease. Ligamentous or muscular strain can cause pain when the patient bends contralaterally.

**C.Motor, sensory and reflex function** should be assessed to determine the affected nerve root level. Muscle strength is graded from zero (no evidence of contractility) to 5 (motion against resistance).

**D.Specific movements and positions that reproduce the symptoms** should be documented. The upper lumbar region (L1, L2 and L3) controls the iliopsoas muscles, which can be evaluated by testing resistance to hip flexion. While seated, the patient should attempt to raise each thigh while the physician's hands are placed on the leg to create resistance. Pain and weakness are indicative of upper lumbar nerve root involvement. The L2, L3 and L4 nerve roots control the quadriceps muscle, which can be

evaluated by manually trying to flex the actively extended knee. The L4 nerve root also controls the tibialis anterior muscle, which can be tested by heel walking.

**E.The L5 nerve root** controls the extensor hallucis longus, which can be tested with the patient seated and moving both great toes in a dorsiflexed position against resistance. The L5 nerve root also innervates the hip abductors, which are evaluated by the Trendelenburg test. This test requires the patient to stand on one leg; the physician stands behind the patient and puts his or her hands on the patient's hips. A positive test is characterized by any drop in the pelvis and suggests L5 nerve root pathology.

**F.Cauda equina syndrome** can be identified by unexpected laxity of the anal sphincter, perianal or perineal sensory loss, or major motor loss in the lower extremities.

**G.Nerve root tension signs** are evaluated with the straight-leg raising test in the supine position. The physician raises the patient's legs to 90 degrees. If nerve root compression is present, this test causes severe pain in the back of the affected leg and can reveal a disorder of the L5 or S1 nerve root.

**H.The most common sites for a herniated lumbar disc** are L4-5 and L5-S1, resulting in back pain and pain radiating down the posterior and lateral leg, to below the knee.

**I.A crossed straight-leg raising test** may suggest nerve root compression. In this test, straight-leg raising of the contralateral limb reproduces more specific but less intense pain on the affected side. In addition, the femoral stretch test can be used to evaluate the reproducibility of pain. The patient lies in either the prone or the lateral decubitus position, and the thigh is extended at the hip, and the knee is flexed. Reproduction of pain suggests upper nerve root (L2, L3 and L4) disorders.

**Indications for Radiographs in the Patient with Acute Low Back Pain**

History of significant trauma
Neurologic deficits
Systemic symptoms
Temperature greater than 38°C (100.4°F)
Unexplained weight loss
Medical history
- Cancer
- Corticosteroid use
- Drug or alcohol abuse

Ankylosing spondylitis suspected

| Differential Diagnosis of Acute Low Back Pain | | | | | |
|---|---|---|---|---|---|
| **Disease or condition** | **Patient age (years)** | **Location of pain** | **Quality of pain** | **Aggravating or relieving factors** | **Signs** |
| Back strain | 20 to 40 | Low back, buttock, posterior thigh | Ache, spasm | Increased with activity or bending | Local tenderness, limited spinal motion |
| Acute disc herniation | 30 to 50 | Low back to lower leg | Sharp, shooting or burning pain, paresthesia in leg | Decreased with standing; increased with bending or sitting | Positive straight leg raise test, weakness, asymmetric reflexes |
| Osteoarthritis or spinal stenosis | >50 | Low back to lower leg; often bilateral | Ache, shooting pain, "pins and needles" sensation | Increased with walking, especially up an incline; decreased with sitting | Mild decrease in extension of spine; may have weakness or asymmetric reflexes |
| Spondylolisthesis | Any age | Back, posterior thigh | Ache | Increased with activity or bending | Exaggeration of the lumbar curve, palpable "step off" (defect between spinous processes), tight hamstrings |
| Ankylosing spondylitis | 15 to 40 | Sacroiliac joints, lumbar spine | Ache | Morning stiffness | Decreased back motion, tenderness over sacroiliac joints |
| Infection | Any age | Lumbar spine, sacrum | Sharp pain, ache | Varies | Fever, percussive tenderness; may have neurologic abnormalities or decreased motion |
| Malignancy | >50 | Affected bone(s) | Dull ache, throbbing pain; slowly progressive | Increased with recumbency or cough | May have localized tenderness, neurologic signs or fever |

| Waddell Signs: Nonorganic Signs Indicating the Presence of a Functional Component of Back Pain |
|---|
| Superficial, nonanatomic tenderness<br>Pain with simulated testing (eg, axial loading or pelvic rotation)<br>Inconsistent responses with distraction (eg, straight leg raises while the patient is sitting)<br>Nonorganic regional disturbances (eg, nondermatomal sensory loss)<br>Overreaction |

**Location of Pain and Motor Deficits in Association with Nerve Root Involvement**

| Disc level | Location of pain | Motor deficit |
|---|---|---|
| T12-L1 | Pain in inguinal region and medial thigh | None |
| L1-2 | Pain in anterior and medial aspect of upper thigh | Slight weakness in quadriceps; slightly diminished suprapatellar reflex |
| L2-3 | Pain in anterolateral thigh | Weakened quadriceps; diminished patellar or suprapatellar reflex |
| L3-4 | Pain in posterolateral thigh and anterior tibial area | Weakened quadriceps; diminished patellar reflex |
| L4-5 | Pain in dorsum of foot | Extensor weakness of big toe and foot |
| L5-S1 | Pain in lateral aspect of foot | Diminished or absent Achilles reflex |

**J.Laboratory tests**

**1.**Evaluation may include a complete blood count, determination of erythrocyte sedimentation rate.

**2.Radiographic evaluation**. Plain-film radiography is rarely useful in the initial evaluation of patients with acute-onset low back pain. Plain-film radiographs are normal or equivocal in more than 75 percent of patients with low back pain. Views of the spine uncover useful information in fewer than 3 percent of patients. Anteroposterior and lateral radiographs should be considered in patients who have a history of trauma, neurologic deficits, or systemic symptoms.

**3.Magnetic resonance imaging and computed tomographic scanning**

**a.**Magnetic resonance imaging (MRI) and computed tomographic (CT) scanning often demonstrate abnormalities in "normal" asymptomatic people. Thus, positive findings in patients with back pain are frequently of questionable clinical significance.

**b.**MRI is better at imaging soft tissue (eg, herniated discs, tumors). CT scanning provides better imaging of bone (eg, osteoarthritis). MRI has the ability to demonstrate disc damage. MRI or CT studies should be considered in patients with worsening neurologic deficits or a suspected systemic cause of back pain such as infection or neoplasm.

**4.Bone scintigraphy** or bone scanning, can be useful when radiographs of the spine are normal, but the clinical findings are suspicious for osteomyelitis, bony neoplasm or occult fracture.

**5.Physiologic assessment**. Electrodiagnostic assessments such as needle electromyography and nerve conduction studies are useful in differentiating peripheral neuropathy from radiculopathy or myopathy.

**III.Management of acute low back pain**

**A.Pharmacologic therapy**

**1.**The mainstay of pharmacologic therapy for acute low back pain is acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID). If no medical contraindications are present, a two- to four-week course of medication at anti-inflammatory levels is suggested.

**2.**Naproxen (Naprosyn) 500 mg, followed by 250 mg PO tid-qid prn [250, 375,500 mg].

**3.**Naproxen sodium (Aleve) 200 mg PO tid prn.

**4.**Naproxen sodium (Anaprox) 550 mg, followed by 275 mg PO tid-qid prn.

**5.**Ibuprofen (Motrin, Advil) 800 mg, then 400 mg PO q4-6h prn.

**6.**Diclofenac (Voltaren) 50 mg bid-tid or 75 mg bid.

**7.**Gastrointestinal prophylaxis, using a histamine $H_2$ antagonist or misoprostol (Cytotec), should be prescribed for patients who are at risk for peptic ulcer disease.

**8.**Rofecoxib (Vioxx) and celecoxib (Celebrex) are NSAIDs with selective cyclo-oxygenase-2 inhibition. These agents have fewer gastrointestinal side effects.

**9.**Celecoxib (Celebrex) is given as 200 mg qd or 100 mg bid.

**10.**Rofecoxib (Vioxx) is given as 25-50 mg qd.

**11.**For relief of acute pain, short-term use of a narcotic may be considered.

**B.Rest.** Two to three days of bed rest in a supine position may be recommended for patients with acute radiculopathy.

**C.Physical therapy modalities**

**1.**Superficial heat, ultrasound (deep heat), cold packs and massage are useful for relieving symptoms in the acute phase after the onset of low back pain.

**2.** No convincing evidence has demonstrated the long-term effectiveness of lumbar traction and transcutaneous electrical stimulation.

**D. Aerobic exercise** has been reported to improve or prevent back pain. Exercise programs that facilitate weight loss, trunk strengthening and the stretching of musculotendinous structures appear to be most helpful. Exercises should promote the strengthening of muscles that support the spine.

**E. Trigger point injections** can provide extended relief for localized pain sources. An injection of 1 to 2 mL of 1 percent lidocaine (Xylocaine) without epinephrine is usually administered. Epidural steroid injection therapy has been reported to be effective in patients with lumbar disc herniation.

**F. Indications for herniated disc surgery.** Most patients with a herniated disc may be effectively treated conservatively. Indications for referral include the following: (1) cauda equina syndrome, (2) progressive neurologic deficit, (3) profound neurologic deficit and (4) severe and disabling pain refractory to four to six weeks of conservative treatment.

**References:** See page 255.

## Osteoarthritis

Approximately 40 million Americans of all ages are affected by osteoarthritis and 70 to 90 percent of Americans older than 75 years have at least one involved joint. The prevalence of osteoarthritis ranges from 30 to 90 percent.

**Clinical Features of Osteoarthritis**

| **Symptoms** | **Pattern of joint involvement** |
|---|---|
| Joint pain<br>Morning stiffness lasting less than 30 minutes<br>Joint instability or buckling<br>Loss of function | **Axial:** cervical and lumbar spine<br>**Peripheral:** distal interphalangeal joint proximal interphalangeal joint first carpometacarpal joints, knees, hips |
| **Signs** | |
| Bony enlargement at affected joints<br>Limitation of range of motion<br>Crepitus on motion<br>Pain with motion<br>Malalignment and/or joint deformity | |

**I. Clinical evaluation**

**A. Pathogenesis.** Osteoarthritis is caused by a combination of mechanical, cellular, and biochemical processes leading to changes in the composition and mechanical properties of the articular cartilage and degenerative changes and an abnormal repair response.

**B.** The typical patient with osteoarthritis is middle-aged or elderly and complains of pain in the knee, hip, hand or spine. The usual presenting symptom is pain involving one or only a few joints. Joint involvement is usually symmetric. The patient usually has pain, stiffness, and some limitation of function. Pain typically worsens with use of the affected joint and is alleviated with rest. Morning stiffness lasting less than 30 minutes is common. (morning stiffness in rheumatoid arthritis lasts longer than 45 minutes.)

**C.** Patients with osteoarthritis of the hip may complain of pain in the buttock, groin, thigh or knee. Hip stiffness is common, particularly after inactivity. Involvement of the apophyseal or facet joints of the lower cervical spine may cause neck symptoms, and involvement of the lumbar spine may cause pain in the lower back. Patients may have radicular symptoms, including pain, weakness and numbness.

**D.** The physical examination should include an assessment of the affected joints, surrounding soft tissue and bursal areas. Joint enlargement may become evident. Crepitus, or a grating sensation in the joint, is a late manifestation.

**E.** Laboratory work may include erythrocyte sedimentation rate and rheumatoid factor. Synovial fluid analysis may be conducted to help exclude other diagnoses.

**F.** Radiographic findings consistent with osteoarthritis include presence of joint space narrowing, osteophyte formation, pseudocyst in subchondral bone, and increased density of subchondral bone. The absence of radiographic changes does not exclude the diagnosis of osteoarthritis. Radiographs are recommended for patients with trauma, joint pain at night, progressive joint pain, significant family history of inflammatory arthritis, and children younger than 18 years.

**II. Treatment of osteoarthritis**

**A. Exercise.** The goals of an exercise program are to maintain range of motion, muscle strength and general health.

**Management of Osteoarthritis of the Knee**

1. Patient education, exercise, weight loss, joint protection
2. Acetaminophen (Tylenol), up to 4 g per day.
3. Add topical capsaicin cream (eg ArthriCare) applied four times daily if needed.
4. If joint effusion is present consider aspiration and intra-articular injection of triamcinolone (Aristocort) 40 mg.
5. If more pain or symptom control is needed add an NSAID, 400 mg of ibuprofen (eg Advil) taken four times daily or a nonacetylated salicylate such as choline magnesium trisalicylate (Trilisate), 500-1500 mg bid, or salsalate (Disalcid), 500-1000 mg tid.
6. If more pain or symptom control is needed use the full dosage of an NSAID plus misoprostol (Cytotec) or a proton pump inhibitor if the patient is at risk for upper gastrointestinal tract bleeding or ulcer disease, or substitute a cyclo-oxygenase-2 inhibitor for the NSAID; some patients may benefit from intra-articular injections of a hyaluronic acid-like product.
7. If the response is inadequate, consider joint lavage, arthroscopic debridement osteotomy, or joint replacement.

**Risk Factors for Ulcer Complications Induced by Nonsteroidal Anti-inflammatory Drugs**

| Definite risk factors | Possible risk factors |
|---|---|
| Patient older than 65 years of age | Female gender |
| Previous ulcer disease or upper gastrointestinal tract bleeding | Smoking |
| Use of a high dosage of one of these drugs | Alcohol consumption |
| Concomitant oral corticosteroid therapy | Helicobacter pylori infection |
| Concomitant anticoagulant therapy | |
| Duration of therapy (risk is higher in first three months of treatment) | |

**B.** The risk of NSAID-induced renal and hepatic toxicity is increased in older patients and in patients with preexisting renal or hepatic insufficiency. Thus, it is important to monitor renal and liver function. Choline magnesium trisalicylate (Trilisate) and salsalate (Disalcid) cause less renal toxicity. Liver function tests and serum hemoglobin, creatinine and potassium measurements should be performed before NSAID therapy is initiated and again after six months of treatment.

**C. Cyclooxygenase-2 (COX-2) inhibitors**

**1. Celecoxib (Celebrex)** is a COX-2 inhibitor labeled for treatment of osteoarthritis and rheumatoid arthritis. Celecoxib effectively alleviates pain and reduces inflammation, but it does not cause gastric ulcers or affect platelet function (two toxic effects associated with COX-1 inhibitors). The most common side effects of celecoxib are dyspepsia, diarrhea and abdominal pain. The FDA has labeled celecoxib, 100 mg twice daily and 200 mg once daily, for the treatment of osteoarthritis. This drug is also labeled, in a dosage of 100 to 200 mg twice daily, for the treatment of rheumatoid arthritis in adults.

**2. Rofecoxib (Vioxx)** is also given once daily for the treatment of osteoarthritis and acute pain. The FDA has labeled rofecoxib for the treatment of primary dysmenorrhea, acute pain, and osteoarthritis. For osteoarthritis, the recommended dosage of rofecoxib is 12.5 to 25 mg once daily. For acute pain and primary dysmenorrhea, the dosage is 50 mg once daily.

**3. Meloxicam (Mobic)** has been labeled by the FDA for the treatment of osteoarthritis. The starting and maintenance dosage is 7.5 mg per day.

**4. Valdecoxib (Bextra)** is an COX-2 inhibitor for treating arthritis and menstrual pain.

**Costs of Some Common Nonsteroidal Anti-inflammatory Drugs**

| Drug | Usual dosage for adults | Formulations |
|---|---|---|
| **Acetic acids** | | |
| Diclofenac potassium (Cataflam) | 100 to 200 mg daily | 50 mg |
| Diclofenac sodium Immediate-release (Voltaren) | 100 to 200 mg daily | 25, 50, 75 mg |
| Delayed-release (Voltaren XR) | 100 to 200 mg daily | 100 mg |
| With misoprostol (Arthrotec) | 50 mg three times daily<br><br>50 mg three or four times daily for rheumatoid arthritis | 50 mg diclofenac sodium with 200 µg misoprostol<br>75 mg diclofenac sodium with 200 µg misoprostol |

| Drug | Usual dosage for adults | Formulations |
|---|---|---|
| Etodolac Immediate-release (Lodine) | 600 to 1,000 mg daily given in two divided doses | 200 mg<br>300 mg<br>400 mg<br>500 mg |
| Extended-release (Lodine XL) | 400 to 1,000 mg daily | 400 mg<br>500 mg<br>600 mg |
| Sulindac (Clinoril) | 150 mg twice daily (maximum dosage: 400 mg daily) | 150, 200 mg |
| **Propionic acids** | | |
| Flurbiprofen (Ansaid) | 200 to 300 mg daily given in two to four divided doses | 50, 100 mg |
| Ibuprofen (Motrin) | 400 to 800 mg three or four times daily (maximum dosage: 3,200 mg daily) | 200 mg<br>400 mg<br>600 mg<br>800 mg |
| Ketoprofen Immediate-release (Orudis) | 150 to 300 mg daily given in three to four divided doses | 25 mg<br>50 mg<br>75 mg |
| Extended-release (Oruvail) | 150 to 300 mg daily given in three or four divided doses | 100 mg<br>150 mg<br>200 mg |
| Over-the-counter (Orudis KT) | 12.5 mg every 4 to 6 hours | 12.5 mg |
| Naproxen Immediate-release (Naprosyn) | 250 to 500 mg twice daily | 250 mg<br>375 mg<br>500 mg |
| Delayed-release (EC Naprosyn) | 750 or 1,000 mg daily | 375 mg<br>500 mg |
| Naproxen sodium Immediate-release (Anaprox, Anaprox DS) | 275 or 550 mg twice daily | 275 mg<br>550 mg |
| Extended-release (Naprelan) | 750 or 1,000 mg daily | 375 mg<br>500 mg |
| Over-the-counter (Aleve) | 220 mg every 8 to 12 hours | 220 mg |
| Oxaprozin (Daypro) | 1,200 mg daily | 600 mg |
| **Nonacidic agents** | | |
| Nabumetone (Relafen) | 1,000 to 2,000 mg given once daily or twice daily in divided doses | 500 mg<br>750 mg |
| **Cyclooxygenase-2 inhibitors** | | |
| Celecoxib (Celebrex) | 100 mg twice daily or 200 mg daily for osteoarthritis<br>100 to 200 mg twice daily for rheumatoid arthritis | 100 mg<br>200 mg |
| Rofecoxib (Vioxx) | 12.5 to 25 mg daily for osteoarthritis<br>50 mg daily for primary dysmenorrhea and acute pain | 12.5 mg<br>25 mg<br>50 mg<br>12.5 or 25 mg in 5-mL susp |
| Valdecoxib (Bextra) | 10-20 mg once daily | 10 mg<br>20 mg |

**D.Local analgesics.** Capsaicin (eg, ArthriCare) has been shown to be better than placebo in osteoarthritis. Capsaicin cream is available over the counter in concentrations of 0.025, 0.075 and 0.25 percent.

**E.Intra-articular corticosteroid injections.** Patients with a painful flare of osteoarthritis of the knee may benefit from intra-articular injection of triamcinolone (Aristocort) or prednisone 8-20 mg. Intra-articular steroid injections should not be administered more than three to four times per year. Knee injections significantly reduce pain for up to four weeks.

**F.Intra-articular injections of hyaluronic acid-like products.** Hyaluronate (Hyalgan) and hylan G-F 20 (Synvisc) injections are useful for the treatment of

osteoarthritis of the knee. Hylan G-F 20 injections are at least as effective as continuous NSAID therapy.

**G.Surgery.** Patients whose symptoms are not adequately controlled with medical therapy and who have moderate to severe pain and functional impairment are candidates for surgery. Osteoarthritis of the knee may be treated with arthroscopic debridement or joint lavage.

**References:** See page 255.

## Gout

Gout comprises a heterogeneous group of disorders characterized by deposition of uric acid crystals in the joints and tendons. Gout has a prevalence of 5.0 to 6.6 cases per 1,000 men and 1.0 to 3.0 cases per 1,000 women.

**I.Clinical features**

**A.Asymptomatic hyperuricemia** is defined as an abnormally high serum urate level, without gouty arthritis or nephrolithiasis. Hyperuricemia is defined as a serum urate concentration greater than 7 mg/dL. Hyperuricemia predisposes patients to both gout and nephrolithiasis, but therapy is generally not warranted in the asymptomatic patient.

**B.Acute gout** is characterized by the sudden onset of pain, erythema, limited range of motion and swelling of the involved joint. The peak incidence of acute gout occurs between 30 and 50 years of age. First attacks are monoarticular in 90 percent. In more than one-half of patients, the first metatarsophalangeal joint is the initial joint involved, a condition known as podagra. Joint involvement includes the metatarsophalangeal joint, the instep/forefoot, the ankle, the knee, the wrist and the fingers.

**C.Intercritical gout** consists of the asymptomatic phase of the disease following recovery from acute gouty arthritis.

**D.Recurrent gouty arthritis.** Approximately 60 percent of patients have a second attack within the first year, and 78 percent have a second attack within two years.

**E.Chronic tophaceous gout.** Tophi are deposits of sodium urate that are large enough to be seen on radiographs and may occur at virtually any site. Common sites include the joints of the hands or feet, the helix of the ear, the olecranon bursa, and the Achilles tendon.

**II.Diagnosis**

**A.**Definitive diagnosis of gout requires aspiration and examination of synovial fluid for monosodium urate crystals. Monosodium urate crystals are identified by polarized light microscopy.

**B.**If a polarizing microscope is not available, the characteristic needle shape of the monosodium urate crystals, especially when found within white blood cells, can be identified with conventional light microscopy. The appearance resembles a toothpick piercing an olive.

**III.Treatment of gout**

**A.Asymptomatic hyperuricemia.** Urate-lowering drugs should not be used to treat patients with asymptomatic hyperuricemia. If hyperuricemia is identified, associated factors such as obesity, hypercholesterolemia, alcohol consumption and hypertension should be addressed.

**B.Acute gout**

**1.**NSAIDs are the preferred therapy for the treatment of acute gout. Indomethacin (Indocin), ibuprofen (Motrin), naproxen (Naprosyn), sulindac (Clinoril), piroxicam (Feldene) and ketoprofen (Orudis) are effective. More than 90 percent of patients have a resolution of the attack within five to eight days.

**Drugs Used in the Management of Acute Gout**

| Drug | Dosage | Side effects/comments |
|---|---|---|
| **NSAIDS** | | |
| Indomethacin (Indocin)<br>Naproxen (Naprosyn)<br>Ibuprofen (Motrin)<br>Sulindac (Clinoril)<br>Ketoprofen (Orudis) | 25 to 50 mg four times daily<br>500 mg two times daily<br>800 mg four times daily<br>200 mg two times daily<br>75 mg four times daily | Contraindicated with peptic ulcer disease or systemic anticoagulation; side effects include gastropathy, nephropathy, liver dysfunction, and reversible platelet dysfunction; may cause fluid overload in patients with heart failure |
| **Corticosteroids** | | |
| Oral | Prednisone, 0.5 mg per kg on day 1, taper by 5.0 mg each day thereafter | Fluid retention; impaired wound healing |
| Intramuscular | Triamcinolone acetonide (Kenalog), 60 mg intramuscularly, repeat in 24 hours if necessary | May require repeat injections; risk of soft tissue atrophy |
| Intra-articular | Large joints: 10 to 40 mg<br>Small joints: 5 to 20 mg | Preferable route for monoarticular involvement |

| Drug | Dosage | Side effects/comments |
|---|---|---|
| ACTH | 40 to 80 IU intramuscularly; repeat every 8 hours as necessary | Repeat injections are commonly needed; requires intact pituitary-adrenal axis; stimulation of mineralocorticoid release may cause volume overload |
| Colchicine | 0.5 to 0.6 mg PO every hour until relief or side effects occur, or until a maximum dosage of 6 mg is reached | Dose-dependent gastrointestinal side effects; improper intravenous dosing has caused bone marrow suppression, renal failure and death |

**2.Corticosteroids**

**a.Intra-articular, intravenous, intramuscular or oral corticosteroids** are effective in acute gout. In cases where one or two joints are involved, intra-articular injection of corticosteroid can be used.

**b.Intramuscular triamcinolone acetonide** (60 mg) is as effective as indomethacin in relieving acute gouty arthritis. Triamcinolone acetonide is especially useful in patients with contraindications to NSAIDs.

**c.Oral prednisone** is an option when repeat dosing is anticipated. Prednisone, 0.5 mg per kg on day 1 and tapered by 5 mg each day is very effective.

**3.Colchicine** is effective in treating acute gout; however, 80 percent of patients experience gastrointestinal side effects, including nausea, vomiting and diarrhea. Intravenous colchicine is available but is highly toxic and not recommended.

**C.Treatment of intercritical gout**

**1.**Prophylactic colchicine (from 0.6 mg to 1.2 mg) should be administered at the same time urate-lowering drug therapy is initiate. Colchicine should be used for prophylaxis only with concurrent use of urate-lowering agents. Colchicine is used for prophylaxis until the serum urate concentration is at the desired level and the patient has been free from acute gouty attacks for three to six months.

**2.Urate-lowering agents**

**a.**After the acute gouty attack is treated and prophylactic therapy is initiated, sources of hyperuricemia should be eliminated to lower the serum urate level without the use of medication.

**b.**Medications that may aggravate the patient's condition (eg, diuretics) should be discontinued; purine-rich foods and alcohol consumption should be curtailed, and the patient should gradually lose weight, if obese.

**Purine Content of Foods and Beverages**

**High**

**Avoid:** Liver, kidney, anchovies, sardines, herring, mussels, bacon, codfish, scallops, trout, haddock, veal, venison, turkey, alcoholic beverages

**Moderate**

**May eat occasionally:** Asparagus, beef, bouillon, chicken, crab, duck, ham, kidney beans, lentils, lima beans, mushrooms, lobster, oysters, pork, shrimp, spinach

**3.24-hour urine uric acid excretion measurement** is essential to identify the most appropriate urate-lowering medication and to check for significant preexisting renal insufficiency.

**a.**Uricosuric agents should be used in most patients with gout because most are "underexcretors" of uric acid. Inhibitors of uric acid synthesis are more toxic and should be reserved for use in "overproducers" of urate (urine excretion >800 mg in 24 hours).

**b.**Urate-lowering therapy should not be initiated until the acute attack has resolved, since they may exacerbate the attack.

**Urate-Lowering Drugs for the Treatment of Gout and Hyperuricemia**

| Drug | Dosage | Indications | Side effects/comments |
|---|---|---|---|
| Probenecid (Benemid) | Begin with 250 mg twice daily, gradually titrating upward until the serum urate level is <6 mg per dL; maximum: 3 g per day | Recurrent gout may be combined with allopurinol in resistant hyperuricemia | Uricosuric agent; creatinine clearance must be >60 mL per minute; therapeutic effect reversed by aspirin therapy; avoid concurrent daily aspirin use; contraindicated in urolithiasis; may precipitate gouty attack at start of therapy; rash or gastrointestinal side effects may occur |

| Drug | Dosage | Indications | Side effects/comments |
|---|---|---|---|
| Allopurinol (Zyloprim) | Begin with 50 to 100 mg daily, gradually titrating upward until the serum urate level is <6 mg per dL; typical dosage: 200 to 300 mg daily | Chronic gouty arthritis; secondary hyperuricemia related to the use of cytolytics in the treatment of hematologic malignancies; gout complicated by renal disease or renal calculi | Inhibits uric acid synthesis; side effects include rash, gastrointestinal symptoms, headache, urticaria and interstitial nephritis; rare, potentially fatal hypersensitivity syndrome |

**4.Probenecid (Benemid)** is the most frequently used uricosuric medication. Candidates for probenecid therapy must have hyperuricemia attributed to undersecretion of urate (ie, <800 mg in 24 hours), a creatinine clearance of >60 mL/minute and no history of nephrolithiasis. Probenecid should be initiated at a dosage of 250 mg twice daily and increased as needed, up to 3 g per day, to achieve a serum urate level of less than 6 mg per dL. Side effects include precipitation of an acute gouty attack, renal calculi, rash, and gastrointestinal problems.

**5.Allopurinol (Zyloprim)** is an inhibitor of uric acid synthesis. Allopurinol is initiated at a dosage of 100 mg per day and increased in increments of 50 to 100 mg per day every two weeks until the urate level is <6 mg per dL. Side effects include rash, gastrointestinal problems, headache, urticaria and interstitial nephritis. A hypersensitivity syndrome associated with fever, bone marrow suppression, hepatic toxicity, renal failure and a systemic hypersensitivity vasculitis is rare.

**References:** See page 255.

## Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic, polyarticular, symmetric, inflammatory disease that affects about 2.5 million people in the United States. The disease has a predilection for small proximal joints, although virtually every peripheral joint in the body can be involved. RA strikes women, usually of childbearing age, three times more often than it does men. This process causes the immune system to attack the synovium of various joints, leading to synovitis.

**I.Clinical manifestations**

**A.**RA is a chronic, symmetric polyarthritis. The polyarthritis is often deforming. About 80% of patients describe a slowly progressive onset over weeks or months.

**B.Inflammatory features**

**1.**The joints in RA are swollen, tender, slightly warm, and stiff. Synovial fluid is cloudy and has an increased number of inflammatory white blood cells.

**2.**Patients with RA usually have profound and prolonged morning stiffness. Fatigue, anemia of chronic disease, fever, vasculitis, pericarditis, and myocarditis, are common.

**C.Joint involvement.** RA may begin in one or two joints, but it almost invariably progresses to affect 20 or more. In some cases, joint involvement is nearly symmetric. Initially, the disease typically involves the metacarpophalangeal, proximal interphalangeal, wrist, and metatarsophalangeal joints, either alone or in combination with others.

**D.Proliferative/erosive features.** The inflamed synovial tissue evolves into a thickened, boggy mass known as a pannus. Pannus can eat through joint cartilage and into adjacent bone.

**E.Joint deformity.** Deformities of RA are more likely to be the result of damage to ligaments, tendons, and joint capsule.

**II.Diagnosis**

**A.**RA is a clinical diagnosis. The presence of arthritis excludes the many forms of soft tissue rheumatism (eg, tendinitis, bursitis). The degree of inflammation excludes osteoarthritis and traumatic arthritis. Polyarticular involvement of the appropriate joints makes the spondyloarthropathies unlikely. The pannus is often palpable as a rubbery mass of tissue around a joint.

**B.Rheumatoid factor testing** helps to confirm the diagnosis of RA. Rheumatoid factor serves as a marker for RA, but it is not reliable because 1-2% of the normal population have rheumatoid factor. Chronic infections, other inflammatory conditions and malignancies may trigger formation of rheumatoid factor. Conversely, 15% of patients with RA are seronegative for rheumatoid factor.

**C.Radiography.** Typical erosions around joint margins help confirm the diagnosis of RA.

**III.Treatment of rheumatoid arthritis**

**IV.Mild disease**

**A.NSAIDs.** Appropriate initial therapy of patients with mild disease consists of an NSAID at full therapeutic dose.

**1.**Initial therapy consists of an NSAID rather than a salicylate, because fewer tablets are required each day. Full anti-inflammatory doses should be administered, such as the equivalent of 3200 mg of ibuprofen,1000 mg of naproxen (Naprosyn), or 200 mg of celecoxib (Celebrex) per day in divided doses, or a single-daily

dose of longer-acting agents, such as piroxicam (Feldene,10 mg bid or 20 mg qd) and rofecoxib (Vioxx, 25-50 mg qd) may be used.

**2.**Selective COX-2 inhibitors, which have equivalent efficacy to NSAIDs but markedly lower gastroduodenal toxicity, are recommended for patients with a history of peptic ulcer, gastrointestinal bleeding, or gastrointestinal intolerance to NSAIDs (including salicylates); rofecoxib (Vioxx, 25-50 mg qd); celecoxib (Celebrex) 100-200 bid; valdecoxib (Bextra) 10 mg qd.

**B.Disease modifying anti-rheumatic drugs (DMARDs).** The addition of hydroxychloroquine (200 mg BID) or sulfasalazine (1000 mg BID or TID) is frequently employed for mild disease. Sulfasalazine is utilized among those with active synovitis.

**C.Adjunctive therapies.** Additional initial therapies may include:

**1.**Acetaminophen for pain relief

**2.**Patient education concerning joint protection

**3.**Physical therapy to enhance muscle tone and help maintain full range of motion

**4.**Intraarticular injection of steroids. When the disease is oligoarticular, joint injection with a depo-corticosteroid preparation, such as triamcinolone hexacetonide, may lead to prolonged local disease control

**V.Moderate disease**

**A.**Patients presenting with moderate disease should receive DMARD therapy in addition to an NSAID.

**B.NSAIDs.** Full anti-inflammatory doses should be administered, such as the equivalent of 3200 mg of ibuprofen,1000 mg of naproxen (Naprosyn), or 200 mg of celecoxib (Celebrex) per day in divided doses, or a single-daily dose of longer-acting agents, such as piroxicam (Feldene) and rofecoxib (Vioxx) may be used.

**C.DMARDs**

**1.**Hydroxychloroquine (200 mg BID) is initiated if the disease is more mild, or sulfasalazine 1000 BID-TID if the disease is intermediate.

**2.**Methotrexate (MTX) is commonly selected as early therapy for active disease. Methotrexate is used, except in women who may become pregnant and patients with liver disease. The dose is 7.5 mg per week. Folic acid (1 to 2 mg/day) or folinic acid (2.5 to 5 mg per week, 8 to 12 hours after methotrexate) should be administered concurrently to reduce potential MTX toxicity.

**3.**For those with contraindications to the use of methotrexate, the following agents can be considered:

**a.**Leflunomide (Arava) alone

**b.**Etanercept (Enbrel) alone

**c.**Adalimumab (Humira) alone

**d.**Infliximab (Remicade) alone

**e.**Combination of hydroxychloroquine and sulfasalazine

**f.**Anakinra (Kineret) alone

**D.**Begin with either leflunomide or TNF-alpha-blockade in this setting. Leflunomide can cause fetal harm and is contraindicated in women who are or may become pregnant. Etanercept, adalimumab, and infliximab are contraindicated in women who are pregnant or nursing, patients with active infection, and those at high risk of reactivation of tuberculosis unless given prophylactic antituberculous therapy.

**E.Anticytokine therapy.** Etanercept, infliximab, adalimumab, or anakinra alone are alternatives for the patient in whom methotrexate is contraindicated. Addition of one of these agents to ongoing methotrexate therapy is an option for patients with moderate disease.

**Antirheumatic drugs used in treatment of rheumatoid arthritis**

| Drug | Delivery | Dose | Side effects |
|---|---|---|---|
| Methotrexate (Rheumatrex Dose Pack) | PO or SC | 5-20 mg/wk | Marrow suppression, mucositis, hepatotoxicity, pulmonary disease, susceptibility to infection |
| Cyclosporine (Neoral) | PO | 2-4 mg/kg daily | Marrow suppression, renal toxicity, hyperuricemia, susceptibility to infection |
| Azathioprine (Imuran) | PO | 50-250 mg/day | Marrow suppression, GI intolerance, hepatotoxicity, tumors, susceptibility to infection |
| Chlorambucil (Leukeran) | PO | 2-8 mg/day | Marrow suppression (particularly thrombocytopenia), tumors, susceptibility to infection |
| Cyclophosphamide (Cytoxan, Neosar) | PO | 25-150 mg/day | Marrow suppression, hemorrhagic cystitis, transitional cell carcinoma and other tumors, susceptibility to infection |
| Leflunomide (Arava) | PO | 100 mg/day for 3 days, then 20 mg/day | Diarrhea, dyspepsia, rash, alopecia, hepatotoxicity, marrow suppression |

| Drug | Deliv-ery | Dose | Side effects |
|---|---|---|---|
| Infliximab (Remicade) | IV | 10 mg/kg infu-sions sporadi-cally | Susceptibility to infection, autoimmune phenome-non, diarrhea, rash, infu-sion reactions |
| Etanercept (Enbrel) | SC | 25 mg twice/w k | Injection site reactions, upper respiratory tract infections; theoretically, sepsis or tumors |
| Adalimuma b (Humira) | SC | 40 mg, every other week | Injection site reactions, upper respiratory tract infections; theoretically, sepsis or tumors |

**F.Adjunctive therapies**

**1.**If the disease remains active (as demonstrated by inflamed joints) and/or the NSAID has produced toxicity, consider the following:

**2.**Change NSAID

**G.**Add prednisone or prednisolone

**1.**Administer intraarticular steroids

**2.**Prednisone can be added at a dose of up to 7.5 mg/day.

**VI.Severe disease**

**A.NSAIDs.** Therapy initially involves a NSAID in full antiinflammatory doses.

**B.DMARDs**

**1.**Unless contraindicated, methotrexate (MTX) is the DMARD of first choice for those with severe disease. The dose is 7.5 mg per week.

**2.**Folic acid that can competitively inhibit the binding of dihydrofolic acid. Folic acid (1 to 2 mg/day) or folinic acid (2.5 to 5 mg per week, 8 to 12 hours after methotrexate) should be administered concurrently to reduce potential toxicity.

**C.Anticytokine therapy**

**1.Etanercept (Enbrel).** Etanercept is extremely effective in controlling symptoms and slowing the rate of radio-graphic progression in early severe RA (10 or 25 mg twice a week). Etanercept is contraindicated in women who are pregnant or nursing, and in patients with active infection.

**2.Infliximab (Remicade.)** Unlike etanercept, which may be used alone, infliximab, a chimeric anti-TNF monoclonal antibody, is generally given in combination with methotrexate. It is therefore usually reserved for use in patients with moderate or severe disease who tolerate, but have had an inadequate response to, methotrexate.

**3.Adalimumab (Humira).** The fully human anti-TNF monoclonal antibody, adalimumab, administered subcutaneously every two weeks is efficacious and can be used alone or combined with methotrexate treatment for RA.

**4.Anakinra (Kineret).** Anakinra, a human interleukin-1 receptor antagonist, also may be of value in patients with active RA. It can be given alone or in combination with methotrexate. However, anakinra should not be given with anti-TNF therapy due to an increased risk of serious infections.

**D.Prednisone.** If the patient is febrile, toxic or experiencing a rapid decline in function, prednisone (5 to 20 mg/day) is frequently added to the regimen of an NSAID and an DMARD. However, once the patient responds sufficiently, the dose of prednisone should be tapered as rapidly as possible to less than 10 mg/day (usually by 8 to 12 weeks).

**References:** See page 255.

# Dermatologic Disorders

## Acne Vulgaris

Acne vulgaris is a polymorphous skin disorder of the sebaceous follicles that begins around the time of puberty and peaks during the teenage years. Prevalence exceeds 85% in teenagers and then declines to about 8% in 25-to 34-year olds and to 3% in 35- to 44-year-olds. More adolescent boys than girls are afflicted.

**I.Pathophysiology of acne**

**A.**Acne is a disease of the pilosebaceous follicle, most commonly on the face, neck, and upper trunk. Acne vulgaris arises from increased sebum production. Androgenic hormones produced during the pubertal period enlarge sebaceous glands, causing increased sebum production.

**B.**Proliferation of Propionibacterium acnes is felt to play a pivotal role in the pathogenesis of inflammatory acne lesions.

**II.Clinical evaluation.** Acne vulgaris occurs primarily on the face and (to a varying degree) the neck, upper back, chest, and shoulders. Classification is based on the number and predominant type of lesions and on the affected sites. The three distinct types are obstructive acne, inflammatory ache, and acne scars.

**III.Treatment of acne**

**A.**Topical agents are generally preferred for comedonal lesions and for superficial inflammatory acne without scarring. Cream is the vehicle of choice in patients with dry or sensitive skin. Topical gels and solutions contain alcohol and are preferred by those with excessively oily skin.

**B.**Topical comedolytic agents reduce the formation of the microcomedo by reversing abnormal keratinization process duct. These agents are the cornerstone of obstructive acne treatment and an important adjunct in all patients with inflammatory acne.

**1.Topical tretinoin (Retin-A)**, a vitamin A derivative, promotes the drainage of preexisting comedones and reduces the formation of new ones. The full cosmetic benefit may not be apparent for 6-12 weeks. Tretinoin should be applied lightly every night at bedtime. Skin irritation (dryness, erythema, and peeling) is common. Patients should avoid excessive sun exposure or should use a protective sunscreen.

**2.**Tretinoin (Retin-A) is available in creams (0.025%, 0.05%, 0.1%), gels (0.01%, 0.025%), liquid (0.05%), and a microsphere (Retin-A Micro 0.1%). The liquid is the most irritating. Patients with fair or sensitive skin should begin by using the 0.025% cream every other day and gradually increase to daily use at a higher concentration as tolerated. The microsphere reduces the potential for irritation.

**3.Adapalene** (**Differin** 0.1% gel), a naphthoic acid derivative with retinoid activity, is comparable to tretinoin, it appears to be less irritating, and it has anti-inflammatory activity. Adapalene is applied as a thin film daily at bedtime. A therapeutic effect is typically seen within 8-12 weeks. Skin irritation occurs in 10-40% of patients. Users should minimize exposure to sunlight.

**4.Tazarotene** (**Tazorac**, 0.05% and 0.1% gel), a synthetic acetylenic retinoid with comedolytic properties, is FDA-approved for topical treatment of mild-to-moderate facial acne. It is applied every evening. Tazarotene is associated with skin irritation. Tazarotene does not offer any significant advantages over tretinoin or adapalene.

**C.Topical antibiotics** inhibit the growth and activity of P acnes. Choices include clindamycin (Cleocin-T 1% solution, lotion, or gel), erythromycin (A/T/S 2% gel or solution, Erygel 2% gel, Akne-Mycin 2% ointment, T-Stat 2% solution and pads), sulfacetamide (Klaron 10% lotion), and a 3% erythromycin and 5% benzoyl peroxide gel (Benzamycin). Topical antibiotics are applied twice daily. Skin dryness and irritation are the most common side effects. Antibiotic resistance is possible. Resistance is less likely with the erythromycin and benzoyl peroxide combination, making it an option for patients who have developed resistance to other agents.

**D.Benzoyl peroxide** is an antibacterial, agent that may also have mild comedolytic properties. It is available over-the-counter and in prescription formulations (2.5%, 5%, and 10% lotions, creams, and gels). Benzoyl peroxide is typically applied as a thin film, once or twice daily. Mild redness and scaling are common during the first few weeks.

**E.Azelaic acid** (**Azelex** 20% cream), a dicarboxylic acid with combined antimicrobial and comedolytic properties, is FDA-approved for mild-to-moderate inflammatory acne. It is massaged in twice daily. Mild skin irritation occurs in 5-10% of patients. Because azelaic acid does not cause photosensitivity, it is an alternative comedolytic agent for patients who are reluctant to refrain from activities that involve significant exposure to the sun. Hypopigmentation is a rare adverse reaction.

**F.Systemic agents**

**1.**Oral antibiotics are the foundation of moderate-to-severe inflammatory acne treatment because they reduce ductal concentrations of P acnes. Improvement can generally be seen within 2-3 weeks.

**2.Tetracycline** is favored because of its better tolerability and lower incidence of P acnes resistance. It is initiated at a dose of 1-2 g/d in 2-4 divided doses. Tetracycline should be taken on an empty stomach. Many individuals whose acne is controlled can be weaned off oral antibiotics after 6 months of therapy, and then topical antimicrobial therapy can be continued for maintenance.

**3.**Long-term use is considered safe; the most common side effects are gastrointestinal upset and vulvovaginal candidiasis. Gram-negative folliculitis may occur, typically manifested by the sudden appearance of superficial pustular or cystic acne lesions around the nares and flaring out over the cheeks.

**4. Minocycline (Minocin)** and trimethoprim/sulfamethoxazole (TMP/SMX [Bactrim, Septra]) have a place in treating some refractory cases. Minocycline can be particularly valuable for patients with treatment-resistant inflammatory acne. Minocycline, like all tetracyclines, is contraindicated in pregnant women and in children younger than 9 years of age because of potential adverse effects on developing bones and teeth.

**5.**TMP/SMX is prescribed at a dose of 1 regular-strength tablet, qd or bid. Hematologic and dermatologic side effects have restricted its use to patients with severe acne refractory to other antibiotics and to those who develop gram-negative folliculitis secondary to long-term antibiotic therapy.

**G.Hormone therapy** improves acne by suppressing sebum production. A triphasic oral contraceptive pill containing ethinyl estradiol, 35 µg, and norgestimate (Ortho Tri-Cyclen) has been shown to reduce inflammatory acne lesions by 40%.

**H.Oral isotretinoin** (13-cis-retinoic acid [Accutane]) is the only available agent with the potential to cure acne. Most patients are started at 0.5-1 mg/kg qd or bid, typically for 15-20 weeks. Adverse reactions include cheilitis, nose bleeds, dry skin and mucous membranes, and photosensitivity. Less common are arthralgias myalgias, headache, nyctalopia, and, in rare cases, pseudotumor cerebri. Isotretinoin can induce abnormalities in liver, hematologic, and lipid functions. Isotretinoin is a teratogen. Contraception must be ensured.

**I.Comedone extraction** is an office procedure used to disimpact obstructive acne lesions. The obstructing plug can usually be expressed after enlarging the pore with a 25-gauge needle.

**J.**Intralesional corticosteroid injection can rapidly (within 48-72 hours) resolve large or recalcitrant inflammatory acne lesions and reduce the risk for scarring. A 30-gauge needle is used to inject 0.05-0.3 mL of a solution containing triamcinolone acetonide through the pore of the lesion.

**References:** See page 255.

## Contact Dermatitis

Contact dermatitis is an extremely common in the pediatric age group. There are two major forms of contact dermatitis: irritant and allergic. Common causes of irritant contact dermatitis include overbathing, drooling, prolonged contact with moisture and feces in the diaper, and bubble baths.

**I.Clinical evaluation**

**A.**Contact dermatitis usually first appears in infants 2-6 months of age. Infants and children have rashes on the shoulders, chest, abdomen, and back. Infants usually also have a rash on the face, scalp and around the ears. Children older than 18 months old tend to have rashes on the neck and antecubital and popliteal fossae. Contact dermatitis usually resolves by puberty, but it sometimes recurs at times of stress.

**B.**Acute lesions are itchy, red, edematous papules and small vesicles which may progress to weeping and crusting lesions. Chronic rubbing and scratching may cause lichenification and hyperpigmentation.

**C.**Patch testing is useful for evaluation of persistent, localized reactions. It also may be useful in patients who have atopic dermatitis and experience a flare or persistence of disease despite appropriate therapy.

**II.Treatment of contact dermatitis**

**A.Moisture.** Avoidance of excessive bathing, hand washing, and lip licking is recommended. Showers or baths should be limited to no more than 5 minutes. After bathing, patients should apply a moisturizer (Aquaphor, Eucerin, Vaseline) to noninflamed skin.

**B.Contact with irritants**

**1.**Overuse of soap should be discouraged. Use of nonirritating soaps (eg, Dove, Ivory, Neutrogena) should be limited to the axilla, groin, hands, and feet.

**2.**Infants often have bright red exudative contact dermatitis (slobber dermatitis) on the cheeks, resulting from drooling. A corticosteroid will usually bring improvement.

**C.Topical corticosteroids**

**1.**Corticosteroid ointments maintain skin hydration and maximize penetration. Corticosteroid creams may sting when applied to acute lesions.

**2.**Mid- and low-potency topical corticosteroids are used twice daily for chronic, atopic dermatitis. High-potency steroids may be used for flare-ups, but the potency should be tapered after the dermatitis is controlled.

**3.**Use of high-potency agents on the face, genitalia and skinfolds may cause epidermal atrophy ("stretch marks"), rebound erythema, and susceptibility to bruising.

| **Commonly Used Topical Corticosteroids** | |
|---|---|
| **Preparation** | **Size** |
| **Low-Potency Agents** | |
| Hydrocortisone ointment, cream, 1, 2.5% (Hytone) | 30 g |
| **Mild-Potency Agents** | |

| Preparation | Size |
|---|---|
| Alclometasone dipropionate cream, ointment, 0.05% (Aclovate) | 60 g |
| Triamcinolone acetonide cream, 0.1% (Aristocort) | 60 g |
| Fluocinolone acetonide cream, 0.01% (Synalar) | 60 g |
| **Medium-Potency Agents** | |
| Triamcinolone acetonide ointment (Aristocort A), 0.1% | 60 g |
| Betamethasone dipropionate cream (Diprosone), 0.05% | 45 g |
| Mometasone cream 0.1% (Elocon) | 45 g |
| Fluocinolone acetonide ointment, 0.025% (Synalar) | 60 g |
| Hydrocortisone butyrate 0.1% cream, ointment (Locoid) | 45 g |
| Betamethasone valerate cream, 0.1% (Valisone) | 45 g |
| Hydrocortisone valerate cream, ointment, 0.2% (Westcort) | 60 g |
| **High-Potency Agents** | |
| Amcinonide ointment, 0.1% (Cyclocort) | 60 g |
| Betamethasone dipropionate ointment (Diprosone) 0.05% | 45 g |
| Fluocinonide cream, ointment, 0.05% (Lidex) | 60 g |

**4.Allergic reactions to topical corticosteroids** may occur. Mometasone (Elocon) is the least likely to cause an allergic reaction.

**D.Antihistamines**, such as diphenhydramine or hydroxyzine (Atarax), are somewhat useful for pruritus and are sedating. Nonsedating antihistamines, such as cetirizine (Zyrtec), loratadine (Claritin) and fexofenadine (Allegra), are helpful.

**E.Systemic corticosteroids** are reserved for severe, widespread reactions to poison ivy, or for severe involvement of the hands, face, or genitals. Prednisone, 1-2 mg/kg, is given PO and tapered over 10-18 days.

**References:** See page 255.

# Common Skin Diseases

**I.Alopecia Areata**

**A.**Alopecia areata is characterized by asymptomatic, noninflammatory, non-scarring areas of complete hair loss, most commonly involving the scalp, but the disorder may involve any area of hair-bearing skin.

**B.**Auto-antibodies to hair follicles are the most likely cause. Emotional stress is sometimes a precipitating factor. The younger the patient and the more widespread the disease, and the poorer the prognosis.

**C.**Regrowth of hair after the first attack takes place in 6 months in 30% of cases, with 50% regrowing within 1 year, and 80% regrowing within 5 years. Ten to 30% of patients will not regrow hair; 5% progress to total hair loss.

**D.**Lesions are well defined, single or multiple round or oval areas of total hair loss. Typical “exclamation point” hairs (3-10 mm in size with a tapered, less pigmented proximal shaft) are seen at the margins.

**E.Differential diagnosis** includes tinea capitis, trichotillomania, secondary syphilis, and lupus erythematosus.

**F.**A VDRL or RPR test for syphilis should be obtained. A CBC, SMAC, sedimentary rate, thyroid function tests, and antinuclear antibody should be completed to screen for pernicious anemia, chronic active hepatitis, thyroid disease, lupus erythematosus, and Addison's disease.

**G.Therapy.** Topical steroids, intralesional steroids, and topical minoxidil may be somewhat effective.

**1.**Intralesional glucocorticoid injection is the most common therapy for limited involvement. Triamcinolone in a dosage of 10 mg per mL, is the preferred agent.

**2.**Topical therapy may be beneficial when it is combined with minoxidil, anthralin or injected steroids.

**3.**Topical minoxidil, 5 percent solution, is 40% effective in stimulating hair growth on the scalp, eyebrows and beard area. Minoxidil solution is applied twice daily and stimulates hair growth within 12 weeks.

**4.**Anthralin cream is commonly used in children. New hair growth may occur within two to three months after initiation of topical anthralin therapy. In one study, 25 percent of patients had cosmetically acceptable results by six months. Side effects of anthralin include redness, itching and scaling. Removal of the cream after application for 20 to 60 minutes is often recommended. However, overnight application has been shown to be well tolerated by some patients.

**5.**The investigational technique called topical immunotherapy, or contact sensitization, may be effective.

**II.Scabies**

**A.**Scabies is an extremely pruritic eruption usually accentuated in the groin, axillae, navel, breasts and finger webs, with sparing the head.

**B.**Scabies is spread by skin to skin contact. The diagnosis is established by finding the mite, ova, or feces in scrapings of the skin, usually of the finger webs or genitalia.

**C.**Treatment of choice for nonpregnant adults and children is lindane (Kwell), applied for 12 hours, then washed off.

**D.**Elimite, a 5% permethrin cream, applied liberally head to toe and rinsed off in 12 hours, is more effective but more expensive than lindane (Kwell).

**E.**Treatment should be given to all members of an infected household simultaneously. Clothing and sheets must be washed on the day of treatment.

**III.Acne Rosacea**

**A.**This condition commonly presents in fair-skinned individuals and is characterized by papules, erythema, and telangiectasias.

**B.**Initial treatment consists of doxycycline or tetracycline. Once there has been some clearing, topical metronidazole gel (Metro-gel) can prevent remission. Sunblock should be used because sunlight can exacerbate the condition.

**IV.Drug Eruptions**

**A.**Drug eruptions may be type I, type II, type III, or type IV immunologic reactions. Cutaneous drug reactions may start within 7 days of initiation of the drug or within 4-7 days after the offending drug has been stopped.

**B.**The cutaneous lesions usually become more severe and widespread over the following several days to 1 week and then clear over the next 7-14 days.

**C.**Lesions most often start first and clear first from the head and upper extremities to the trunk and lower legs. Palms, soles, and mucous membranes may be involved.

**D.**Most drug reactions appear as a typical maculopapular drug reaction. Tetracycline is associated with a fixed drug eruption. Thiazide diuretics have a tendency for photosensitivity eruptions.

**E.Treatment of drug eruptions**

**1.**Oral antihistamines are very useful. Diphenhydramine (Benadryl), 25-50 mg q4-6h. Soothing, tepid water baths in Aveeno or corn starch or cool compresses are useful.

**2.Severe signs and symptoms.** A 2-week course of systemic steroids (prednisone starting at 60 mg/day and then tapering) will usually stop the symptoms.

**F.Erythema Multiforme**

**1.**Erythema multiforme presents as dull red macules or papules on the back of hands, palms, wrists, feet, elbows and knees. The periphery is red and the center becomes blue or darker red, hence the characteristic target or iris lesion.

**2.**The rash is most commonly a drug reaction caused by sulfa medications or phenytoin (Dilantin). It is also seen as a reaction to herpes simplex virus infections, mycoplasma, and Hepatitis B.

**3.**Erythema multiforme major or Steven's Johnson syndrome is diagnosed when mucous membrane or eye involvement is present.

**4.**Prednisone 30-60 mg/day is often given with a 2-4 week taper.

**5.**For HSV-driven erythema multiforme, acyclovir may be helpful. Ophthalmologic consultation is obtained for ocular involvement.

**V.Pityriasis Rosea**

**A.**Pityriasis rosea is an acute inflammatory dermatitis characterized by self-limited lesions distributed on the trunk and extremities. A viral cause is hypothesized. It is most common between the ages of 10 and 35.

**B.Clinical manifestations**

**1.**The initial lesion, called the "herald patch," can appear anywhere on the body, and is 2-6 cm in size, and begins a few days to several weeks before the generalized eruption. The hands, face, and feet are usually spared.

**2.**The lesions are oval, and the long axes follow the lines of cleavage. Lesions are 2 cm or less, pink, tan, or light brown. The borders of the lesions have a loose rim of scales, peeling peripherally, called the "collarette." Pruritus is usually minimal.

**C.Differential diagnosis.** Secondary syphilis (a VDRL is indicated for atypical rashes), drug eruptions, viral exanthems, acute papular psoriasis, tinea corporis.

**D.Treatment.** Topical antipruritic emollients (Caladryl) relieve itching. Ultraviolet therapy may be used. The disease usually resolves in 2-14 weeks and recurrences are unusual.

**References:** See page 255.

# Seborrheic Dermatitis

Seborrheic dermatitis is a chronic inflammatory skin disorder generally confined to areas of the head and trunk. When seborrheic dermatitis occurs in the neonatal period, it usually disappears by six to 12 months of age. Seborrheic dermatitis usually occurs after puberty. Pityrosporum ovale, a yeast, has been implicated in this condition.

**I.Clinical Manifestations**

**A.**Seborrheic dermatitis typically is symmetric, and common sites of involvement are the scalp margin, eyebrows, eyelashes, mustache and beard. Other common sites are the forehead, the nasolabial folds, the external ear canals, the postauricular creases, and the trunk.

**B.**Seborrheic dermatitis causes dandruff, a fine, powdery white scale on the scalp. More severe seborrheic dermatitis is characterized by erythematous plaques with powdery or greasy scale.

**C.Treatment of Scalp and Beard Areas**

**1.**Seborrheic dermatitis is often effectively treated by shampooing daily or every other day with antidandruff shampoos containing 2.5 percent selenium sulfide or 1 to 2 percent pyrithione zinc. Ketoconazole shampoo may also be used. Topical terbinafine solution, 1 percent, has also been shown to be effective.

**2.**If the scalp is covered with diffuse, dense scale, the scale may first be removed by applying mineral oil or olive oil and washing. An alternative is coal tar-keratolytic combination or phenol-saline solution.

**3.**Extensive scale with associated inflammation may be treated by moistening the scalp and then applying fluocinolone, 0.01 percent in oil, to the entire scalp, covering overnight with a shower cap and shampooing in the morning. Corticosteroid solutions, lotions or ointments may be used once or twice daily.

**4.**As a substitute for daily washing, fluocinolone, 0.01 percent in oil, may be used as a scalp pomade. Other options include a moderate- to mid-potency topical corticosteroid in an ointment. After initial control is attained, fluocinolone, 0.01 percent shampoo (FS Shampoo), can be used as an alternative to or in addition to fluocinolone, 0.01 percent in oil (Derma-Smoothe/FS), for maintenance.

**D.Treatment of the Face.** Ketoconazole cream, 2 percent, may be applied once or twice daily. Hydrocortisone cream 1 percent once or twice daily will reduce erythema and itching.

**E.Treatment of the Body.** Seborrhea of the trunk may be treated with zinc or coal tar shampoos or by washing with zinc soaps. Additionally, topical ketoconazole cream, 2 percent, and/or a topical corticosteroid cream, lotion or solution may be applied once or twice daily.

**F.Treatment of Severe Seborrhea.** An occasional patient with severe seborrhea that is unresponsive to topical therapy may be a candidate for isotretinoin therapy. Treatment with daily doses of isotretinoin as low as 0.1 to 0.3 mg per kg may result in improvement in severe seborrhea.

**References:** See page 255.

## Dermatophyte (Tinea) Infections

Superficial fungal infections can be divided into dermatophytic infections, tinea versicolor, and cutaneous candidiasis. Up to 20% of the US population is infected with dermatophytes. Dermatophytes are the most common type of fungi that cause infection of the skin and nails. Three types of superficial fungi/dermatophytes account for the majority of infections: Epidermophyton, Trichophyton, and Microsporum. The fungi attack skin, nails, and hair.

**I.Tinea Capitis**

**A.**Tinea capitis, ringworm of the scalp, almost always occurs in small children. Tinea capitis can occur in two forms, "gray patch" and "black dot." Black dot tinea capitis is the form predominantly seen in the United States.

**B.Gray patch tinea capitis (GPTC)** is usually contracted from cats and dogs. Person-to-person spread is rare.

**1.**The infection begins with an erythematous, scaling, well-demarcated lesion on the scalp that spreads centrifugally for a few weeks or months and persists indefinitely.

**2.**The inflammation subsides, and the hairs within the patch break off a millimeter or two above the level of the scalp. The hair stubs take on a frosted appearance. In a few cases the lesions change abruptly to become boggy, elevated, tender nodules (kerion).

**C.Black dot tinea capitis.**

**1.**Black dot tinea capitis (BDTC) is the most common form of scalp ringworm. It is largely a disease of childhood. All ethnic groups may be infected, but African-American children are particularly susceptible. Spread is usually from child to child contact. Fomites (shared hats, combs, brushes, barrettes, rollers) may play an important role. Asymptomatic carriers in the household may also be involved.

**2.**BDTC usually begins as an asymptomatic, erythematous, scaling patch on the scalp, which slowly enlarges. Hairs within the patches break off. In some cases inflammation is prominent. Left untreated, scarring with permanent alopecia can occur. A sudden transition to kerion may occur.

**D.Diagnosis** of tinea capitis is made by KOH examination of spores on the hair shaft. Diagnosis can be confirmed by culture on Sabouraud's medium.

**E.Treatment**

**1.Griseofulvin (microsize)** remains the drug of choice. Griseofulvin treatment schedules are as follows:

**a.**Adults: 250 mg ultramicrosize by mouth twice daily for 6 to 12 weeks. A few cases of the black dot type may require 250 mg three times daily for the same length of time.

**b.**Children: 20 to 25 mg/kg of body weight for 6 to 12 weeks.

**2.**Terbinafine (Lamisil [250 mg PO QD]) or itraconazole (Sporanox [200 mg per day]) are effective alternatives for resistant cases or for patients who are allergic to griseofulvin.

**3.**Topical treatment of tinea capitis is ineffective. Treatment or removal of an animal is important only when the diagnosis is gray patch tinea capitis.

**4.**Identification of asymptomatic carriers and household fomites is an important part of the management of black dot tinea capitis. Carriers should be treated with selenium sulfide shampoo.

**II.Tinea Pedis**

**A.**Tinea pedis, ringworm of the feet (athlete's foot), is the most common dermatophyte infection. It is often accompanied by tinea manuum, onychomycosis, or tinea cruris. A sterile vesicular eruption often occurs on the palms and fingers, referred to as an "id" reaction. This improves as the primary infection is treated.

**B.**The disease begins as a slowly progressive pruritic, erythematous lesions between the toes. Extension onto the sole follows and later onto the sides or even the top of the foot ("moccasin ringworm"). The normal creases and markings of the skin tend to accumulate scale.

**C.Treatment.** Tinea pedis can usually be treated with a topical antifungal cream for four weeks; interdigital tinea pedis may only require one week of therapy.

**D.Diagnosis.** The diagnosis should be confirmed by KOH examination of scrapings from the lesions. Culture on Sabouraud's medium is also helpful in difficult cases.

**E.**Topical antifungal creams are available over the counter; some prescription agents have a broader spectrum of action and may be administered once instead of twice daily, but all of the creams are equally effective.

**F.**Patients with chronic disease or extensive disease may require oral griseofulvin (250 to 500 mg of microsize BID), terbinafine (Lamisil [250 mg QD]), or itraconazole (Sporanox [200 mg per day]) for four weeks. Terbinafine is more effective than griseofulvin, while the efficacy of terbinafine and itraconazole are similar. Nail involvement is another indication for oral therapy. Secondary infection should be treated with oral antibiotics.

**Topical Antifungal Agents**

| Drug | Dose | supplied |
|---|---|---|
| Terbinafine (Lamisil) | QD to BID | Cream 1%: 15g, 30g<br>Gel 1%: 5g, 15g, 30g |
| Clotrimazole (Lotrimin)* | BID | Cream 1%: 15g, 30g, 45g, 90g<br>Lotion 1%: 30mL<br>Solution 1%: 10mL, 30mL |
| Econazole (Spectazole) | QD (BID for candidiasis) | Cream 196: 15g, 30g, 85g |
| Sulconazole (Exelderm) | QD to BID | Cream 1%: 15g, 30g, 60g<br>Solution 1%: 30mL |
| Oxiconazole (Oxistat) | QD to BID | Cream 1%: 15g, 30g, 60g<br>Lotion 1%: 30mL |
| Naftifine (Naftin) | QD (cream), BID (gel) | Cream 1%: 15g, 30g, 60g<br>Gel 1%: 20g, 40g, 60g |
| Ciclopirox (Loprox) | BID | Cream 1%: 15g, 30g, 90g<br>Lotion 1%: 30mL, 60mL |
| Ketoconazole (Nizoral) | QD | Cream 2%: 15g, 30g, 60g |
| Miconazole (Monistat-Derm)* | BID | Cream 2%: 15g, 30g, 56.7g, 85g |
| Tolnaftate (Tinactin)* | BID | Cream 1% : 15g, 30g<br>Gel 1%: 15g<br>Powder 1%: 45g, 90g<br>Topical aerosol: liquid (1%): 59.2mL, 90mL, 120mL powder (1%):56.7g, 100g, 105g, 150g<br>Solution 1%: 10 mL |

* Also available in over the counter preparations

## III.Onychomycosis

**A.**Onychomycosis refers to nail infections caused by dermatophyte molds (tinea unguium, ringworm of the nails). The great toe is usually the first to be affected. The disease begins with a whitish, yellowish, or brownish discoloration of a distal corner of the nail, which gradually spreads. The distal portion of the nail plate breaks away. Portions of the plate may be heaped up and irregular. The condition persists indefinitely if left untreated.

**B.Diagnosis**

**1.**KOH examination of scrapings from the nail bed to demonstrate hyphae and arthrospores is the best means of diagnosis.

**2.**Cultures (on Sabouraud's medium) are helpful if negative KOH examination is negative. However, results are not available for four to six weeks. The dermatophyte test medium (DTM) culture is an alternative to fungal culture. DTM costs less than culture on Sabouraud's medium, can be performed in the office, and results are available within three to seven days.

**3.Treatment.** Traditional topical therapies are ineffective, and even oral therapy is associated with a high rate of treatment failure and recurrence. Cure rates are better with terbinafine (Lamisil) than itraconazole.

| Oral Antifungal Agents |
|---|
| **Terbinafine (Lamisil):**<br>For fingernails — 250 mg daily by mouth for 6 weeks<br>For toenails — 250 mg daily by mouth for 12 weeks |
| **Itraconazole (Sporanox):**<br>Fixed dosage<br>For fingernails — 200 mg daily by mouth for 8 weeks<br>For toenails — 200 mg daily by mouth for 12 weeks<br>Pulse therapy<br>For fingernails — 400 mg daily by mouth for one week per month for two months<br>For toenails — 400 mg daily by mouth for one week per month for three months |

**IV.Tinea Corporis**

**A.**Tinea corporis begins as a pruritic circular or oval erythematous scaling lesion that spreads centrifugally. Central clearing follows, while the active advancing border, a few millimeters wide, retains its red color and is slightly raised. The result is a lesion shaped like a ring.

**B.Treatment.** Tinea corporis usually responds well to the daily application of topical antifungals such as 1 percent terbinafine cream. Extensive cases and those associated with immunologic compromise are best treated with oral griseofulvin, 250 mg three times daily for 14 days.

**V.Tinea Cruris**

**A.**Tinea cruris (jock itch) is a special form of tinea corporis involving the crural fold. Tinea cruris is far more common in men than women. The disease often begins after physical activity and copious sweating.

**B.**Tinea cruris begins with a macular erythematous lesion high on the inner aspect of one or both thighs, opposite the scrotum. It spreads centrifugally, with partial central clearing and a slightly elevated, erythematous, sharply demarcated border.

**C.Diagnosis.** KOH examination of scales scraped from the lesion will show the segmented hyphae and arthrospores characteristic of all dermatophyte infections. Cultures on Sabouraud's medium can also be used to confirm the diagnosis.

**D.Treatment.** Topical antifungal treatment will usually suffice. One percent terbinafine cream (Lamisil) is a good choice. It should be applied once or twice daily and continued for at least two weeks. Failure to treat concomitant tinea pedis usually results in recurrence. Lesions resistant to topical medications can be treated with griseofulvin 250 mg three times daily by mouth for 14 days. Daily application of talcum, avoidance of hot baths and tight-fitting clothing, and wearing boxer shorts rather than briefs is recommended.

**VI.Tinea Manuum**

**A.**Tinea manuum is an unusual dermatophytic infection of the interdigital and palmar surfaces. It may coexist with other fungal infections, such as tinea pedis. The palmar surface often has diffuse areas of dry, hyperkeratotic skin. Differential diagnosis should include pompholyx, eczema, secondary syphilis, and callus formation.

**B.**The condition often responds to topical therapy.

**VII.Tinea Versicolor**

**A.**Tinea versicolor is common, in young and middle-aged adults. The condition is caused by the lipophilic yeasts, Pityrosporum orbiculare and Pityrosporum ovale. P orbiculare is known as Malassezia furfur. Tinea versicolor is also referred to as pityriasis versicolor.

**B.**Tinea versicolor is typically found on the upper trunk, neck, and arms. The characteristic finding is skin depigmentation, but lesions can range from red to hypopigmented to hyperpigmented.

**C.**Tinea versicolor usually does not clear spontaneously and may persist for many years. "Spotty body" often presents in adolescence and is associated with itching. Tinea versicolor has a high rate of recurrence, and periodic retreatment may be needed.

**D.**Differential diagnosis includes vitiligo, tinea corporis, pityriasis rosea, pityriasis alba, and secondary syphilis.

**E.**Tinea versicolor responds to topical therapies, such as terbinafine, econazole, ketoconazole, and selenium sulfide lotion or shampoo (Exsel, Head & Shoulders, Selsun). Recurrences may be less frequent if a short course of oral itraconazole (Sporanox) is instituted.

**VIII.Cutaneous Candidiasis**

**A.**Cutaneous candidiasis is caused by C albicans. Other candidiasis infections include angular cheilitis (perlèche), erosio interdigitalis blastomycetica, candidal intertrigo, balanitis, vaginitis, and paronychia. Involvement of the skinfolds is most common, but any area of the skin with increased moisture is susceptible.

**B.**Wearing of occlusive clothing, obesity or disorders affecting the immune system (eg, diabetes, AIDS) may increase susceptibility to candidal infection.

**C.**Candidal skin infection often presents with erythema, cracking, or maceration. When maceration develops in the web spaces of the fingers, the skin can become soft and white. Candidal skin infection is characterized by irregular (serrated) edges, tissue erythema, and satellite lesions.

**D.**In patients with normal immunity, candidiasis is most often treated with topical therapy. Commonly used topical agents include nystatin (Mycostatin), ketoconazole, miconazole, and clotrimazole. Therapy with oral fluconazole (Diflucan) is highly effective.

**References:** See page 255.

## Paronychia, Herpetic Whitlow, and Ingrown Toenails

## I. Paronychia

**A.** Paronychia is an inflammation involving the lateral and posterior fingernail folds. Predisposing factors include overzealous manicuring, nail biting, diabetes mellitus, and frequent immersion in water. Paronychia also is associated with antiretroviral therapy for HIV infection.

**B.** Paronychia may be either acute or chronic. Acute paronychia is caused by staphylococcus aureus, and it is characterized by the onset of pain and erythema of the posterior or lateral nail folds, with development of a superficial abscess. Chronic paronychia represents an eczematous condition.

**C. Treatment**

**1. Acute paronychia.** Therapy of acute paronychia includes local care (warm compresses or soaks for 20 minutes, three times per day) and antibiotic therapy. An antistaphylococcal agent such as dicloxacillin (250 mg TID) or cephalexin (Keflex) [500 mg BID to TID]) for seven to ten days is the preferred therapy. An alternative is erythromycin 333 mg TID or azithromycin (Zithromax [500 mg on day one, followed by 250 mg per day for four days]). incision and drainage is necessary if an abscess is present.

**2. Chronic paronychia.** Patients should be advised to keep their hands as dry as possible and to use gloves for all wet work. Patients should avoid irritant or allergen exposure. Chronic paronychia is an eczematous process, and Candida infection is a secondary phenomenon. Thus, the treatment should be a topical corticosteroid, such as triamcinolone 0.1% ointment.

**Comparison of Acute and Chronic Paronychia**

| Features | Acute | Chronic |
|---|---|---|
| Clinical appearance | Red, hot, tender nail folds, with or without abscess | Swollen, tender, red (not as red as acute), boggy nail fold; fluctuance rare |
| People at high risk | People who bite nails, suck fingers, experience nail trauma (manicures) | People repeatedly exposed to water or irritants (e.g., bartenders, housekeepers, dishwashers) |
| Pathogens | Staphylococcal aureus, streptococci, Pseudomonas, anaerobes | Candida albicans (95 percent), atypical mycobacteria, gram-negative rods |
| Treatment | Warm soaks, oral antibiotics (clindamycin [Cleocin] or amoxicillin–clavulanate potassium [Augmentin]); spontaneous drainage, if possible; surgical incision and drainage | Avoidance of water and irritating substances; use of topical steroids and antifungal agents; surgery |

## II. Herpetic Whitlow

**A.** Herpetic whitlow (herpes simplex virus infection of the finger) occurs as a complication of primary oral or genital herpes infection via a break in the skin. It also occurs in medical personnel who have contact with oral secretions. Herpetic whitlow is characterized by erythema, swelling, pain, and vesicular or pustular lesions.

**B.** The diagnosis of herpetic whitlow is suspected by an exposure history as well as the presence of vesicles. Tzanck smear reveals multinucleated giant cells.

**C.** Treatment consists of oral acyclovir (Zovirax [400 mg TID]) for ten days A topical antibiotic cream, such as bacitracin, may help to prevent secondary bacterial infection.

## III. Ingrown Toenail

**A.** Ingrown toenails occur when the lateral nail plate pierces the lateral nail fold. The great toenail is most commonly affected. Signs and symptoms include pain, edema, exudate, and granulation tissue. Predisposing factors include poorly fitting shoes, excessive trimming of the lateral nail plate (pincer nail deformity), and trauma.

**B. Treatment**

**1.** The lateral nail plate should be allowed to grow well beyond the lateral nail fold before trimming horizontally. Patients should wear well-fitting shoes.

**2. Mild-to-moderate lesion**

**a.** Mild-to-moderate lesions are characterized by minimal to moderate pain, little erythema, and no discharge.

**b.** Place a cotton wedging or dental floss underneath the lateral nail plate to separate the nail plate from the lateral nail fold, thereby relieving pressure.

**c.** Soak the affected foot in warm water for 20 minutes, three times per day.

**3. Moderate-to-severe lesion**

**a.** Moderate-to-severe lesions are characterized by substantial erythema and pustular discharge. Treatment consists of the following:

Anesthetize the area with lidocaine 1% without epinephrine.

Using nail-splitting scissors or a hemostat, insert the instrument under the nail plate and remove the involved nail wedge with nail clippers or scissors. Remove any granulation tissue with a curette and/or silver nitrate sticks.

Dilute hydrogen peroxide 1:1 with tap water and cleanse the site 2 or 3 times a day, followed by application of either bacitracin or mupirocin ointment.

**1.Recurrent ingrown toenail.** For patients who suffer recurrent ingrown toenails, consider permanent nail ablation of the lateral nail horn with phenol.

**References:** See page 255.

# Bacterial Infections of the Skin

Bacterial skin infections most commonly include cellulitis, impetigo, and folliculitis.

**I.Cellulitis**

**A.**Cellulitis is a painful, erythematous infection of the dermis and subcutaneous tissues that is characterized by warmth, edema, and advancing borders. Cellulitis commonly occurs near breaks in the skin, such as surgical wounds, trauma, tinea infections, or ulcerations. Patients may have a fever and an elevated white blood cell count. The most common sites of cellulitis are the legs and digits, followed by the face, feet, hands, torso, neck, and buttocks.

**B.**In otherwise healthy adults, isolation of an etiologic agent is difficult and unrewarding. If the patient has diabetes, an immunocompromising disease, or persistent inflammation, blood cultures or aspiration of the area of maximal inflammation may be useful.

**C.Empiric treatment of infection in patients without diabetes:**

**1.Penicillinase-resistant penicillin: Dicloxacillin (Pathocil)** 40 mg/kg/day in 4 divided doses for 7-12 days; adults: 500 mg qid or

**2.First-generation cephalosporin: Cephalexin (Keflex)** 50 mg/kg/day PO in 4 divided doses for 7-10 days; adults: 500 mg PO qid or

**3.Amoxicillin/clavulanate (Augmentin)** 500 mg tid or 875 mg bid for 7-10 days.

**4.Azithromycin (Zithromax)** 500 mg on day 1, then 250 mg PO qd for 4 days.

**5.Erythromycin ethylsuccinate** 40 mg/kg/day in 3 divided doses for 7-10 days; adults: 250-500 mg qid.

**6.**Limited disease can be treated orally, but more extensive disease requires parenteral therapy. Marking the margins of erythema with ink is helpful in following the progression or regression of cellulitis.

**7.**Outpatient therapy with injected ceftriaxone (Rocephin) provides 24 hours of parenteral coverage and may be an option for some patients.

**Descriptions of Bacterial Skin Infections**

| Disease | Description |
|---|---|
| Carbuncle | A network of furuncles connected by sinus tracts |
| Cellulitis | Painful, erythematous infection of deep skin with poorly demarcated borders |
| Erysipelas | Fiery red, painful infection of superficial skin with sharply demarcated borders |
| Folliculitis | Papular or pustular inflammation of hair follicles |
| Furuncle | Painful, firm or fluctuant abscess originating from a hair follicle |
| Impetigo | Large vesicles and/or honey-crusted sores |

**D.**Antibiotics should be maintained for at least three days after the resolution of acute inflammation. Adjunctive therapy includes cool compresses; appropriate analgesics for pain; tetanus immunization; and immobilization and elevation of the affected extremity.

**E.**A parenteral second- or third-generation cephalosporin (with or without an aminoglycoside) should be considered in patients who have diabetes, immunocompromised patients, those with unresponsive infections, or in young children. The patient may also require a plain radiograph of the area or surgical debridement to evaluate for gas gangrene, osteomyelitis, or necrotizing fasciitis.

**F.Periorbital cellulitis** is caused by the same organisms that cause other forms of cellulitis and is treated with warm soaks, oral antibiotics, and close follow-up. Children with periorbital or orbital cellulitis often have underlying sinusitis. If the child is febrile and appears toxic, blood cultures should be performed and lumbar puncture considered.

**G.Orbital cellulitis** occurs when the infection passes the orbital septum and is manifested by proptosis, orbital pain, restricted eye movement, visual disturbances, and concomitant sinusitis. This ocular emergency requires intravenous antibiotics, otorhinolaryngology, and ophthalmologic consultation.

**II.Erysipelas**

**A.**Erysipelas usually presents as an intensely erythematous infection with clearly demarcated raised margins and lymphatic streaking. Common sites are the legs and face.

**B.**Erysipelas is caused almost exclusively by beta-hemolytic streptococcus and thus can be treated with oral or intravenous penicillin, or this infection may be treated the same as cellulitis. Adjunctive treatment and complications are the same as for cellulitis.

**III.Impetigo**

**A.**Impetigo is most commonly seen in children aged two to five years and is classified as bullous or nonbullous. The nonbullous type predominates and presents with an

erosion (sore), cluster of erosions, or small vesicles or pustules that have a honey-yellow crust. Impetigo usually appears in areas where there is a break in the skin, such as a wound, herpes simplex infection, or angular cheilitis.

**B.**The bullous form of impetigo presents as a large thin-walled bulla (2 to 5 cm) containing serous yellow fluid. It often ruptures leaving a denuded area. Both forms of impetigo are primarily caused by *S. aureus* with Streptococcus usually being involved in the nonbullous form.

**C.**An oral antibiotic with activity against *S. aureus* and group A beta-hemolytic streptococcus is warranted in nonlocalized cases.

**1.**Azithromycin (Zithromax) for five days and cephalexin (Keflex) for 10 days have been shown to be effective and well-tolerated.

**2.**Dicloxacillin (Pathocil), 500 mg PO qid for 2 weeks.

**3.**Oxacillin (Prostaphlin) 1-2 gm IV q4-6h.

**4.**Cephalexin (Keflex) 250-500 mg PO qid.

**5.**Amoxicillin/clavulanate (Augmentin) 500 mg tid or 875 mg bid for 7-10 days.

**6.**Broad-spectrum fluoroquinolones have also been shown to be effective for treating skin and soft tissue infections. These medications have excellent skin penetration and good bioavailability.

**IV.Folliculitis**

**A.**The most common form is superficial folliculitis that manifests as a tender or painless pustule that heals without scarring. Multiple or single lesions can appear on any skin bearing hair including the head, neck, trunk, buttocks, and extremities. *S. aureus* is the most likely pathogen. Topical therapy with erythromycin, clindamycin (Cleocin T gel), mupirocin (Bactroban), or benzoyl peroxide can be administered to accelerate the healing process.

**B.**Staphylococci will occasionally invade the deeper portion of the follicle, causing swelling and erythema. These lesions are painful and may scar. This inflammation of the entire follicle or the deeper portion of the hair follicle is called deep folliculitis. Oral antibiotics are usually used and include first-generation cephalosporins, penicillinase-resistant penicillins, macrolides, and fluoroquinolones.

**C.**Gram-negative folliculitis usually involves the face and affects patients with a history of long-term antibiotic therapy for acne. Pathogens include Klebsiella, Enterobacter, and Proteus species. It can be treated as severe acne with isotretinoin (Accutane).

**V.Furuncles and Carbuncles**

**A.**Furuncles and carbuncles occur as a follicular infection progresses deeper and extends out from the follicle. Commonly known as an abscess or boil, a furuncle is a tender, erythematous, firm or fluctuant mass of walled-off purulent material, arising from the hair follicle. The pathogen is usually S. aureus. Typically, the furuncle will develop into a fluctuant mass and eventually open to the skin surface.

**B.**Carbuncles are an aggregate of infected hair follicles that form broad, swollen, erythematous, deep, and painful masses that usually open and drain through multiple tracts. Fever and malaise, are commonly associated with these lesions. With both of these lesions, gentle incision and drainage is indicated when lesions "point" (fluctuant). The wound may be packed (usually with iodoform gauze) to encourage further drainage. In severe cases, parenteral antibiotics such as cloxacillin (Tegopen), or a first-generation cephalosporin, such as cefazolin (Ancef), are required.

**References:** See page 255.

# Psoriasis

Approximately 1 percent of the population is affected by psoriasis. The typical clinical findings of erythema and scaling are the result of hyperproliferation and abnormal differentiation of the epidermis, plus inflammatory cell infiltrates and vascular changes.

**I.Clinical Manifestations**

**A.**Plaque type psoriasis usually presents in young adults with symmetrically distributed plaques involving the scalp, extensor elbows, knees, and back. The plaques are erythematous with sharply defined, raised margins. A thick silvery scale is usually present. The lesions can range from less than 1 cm to more than 10 cm in diameter. The plaques typically are asymptomatic, although some patients complain of pruritus. Inspection may reveal pitting of the nail plates and involvement of intertriginous areas, such as the umbilicus and intergluteal cleft.

**B.Clinical course.** Most patients with psoriasis tend to have the disease for life. However, there may be marked variability in severity over time, and remissions at some stage are seen in 25 percent of cases. Pruritus may be severe and arthritis can be disabling.

**C.Diagnosis.** The diagnosis of psoriasis is made by physical examination and in some cases skin biopsy. The scalp, umbilicus, intergluteal cleft, and nails should be examined.

**II.Treatment**

**A.Topical emollients.** Keeping psoriatic skin soft and moist minimizes itching. The most effective are ointments such as petroleum jelly or thick creams.

**B.Topical corticosteroids**

**1.**Topical corticosteroids remain the mainstay of topical psoriasis treatment despite the development of newer agents.

**2.**In the scalp, potent steroids in an alcohol solution (eg, fluocinonide 0.05 percent) are frequently indicated. On the face and intertriginous areas, a low-potency cream (eg, hydrocortisone 1 percent) should be used.

**3.**For thick plaques on extensor surfaces, potent steroid ointments (eg, betamethasone 0.05 percent) with added occlusion by tape or plastic wrap may be required.

**4.**The typical regimen consists of twice-daily application of topical corticosteroids. Generics include, in order of increasing potency, hydrocortisone (Hytone) 1 percent, triamcinolone (Aristocort) 0.1 percent, fluocinonide (Lidex) 0.05 percent, and betamethasone dipropionate (Diprosone) 0.05 percent.

**5.**Betamethasone valerate in a foam (Luxiq) has superior efficacy for scalp psoriasis.

**Types of Psoriasis, Associated Findings and Treatment Options**

| Type of psoriasis | Clinical features | Differential diagnosis | Treatment options |
|---|---|---|---|
| Plaque-type psoriasis | Red, thick, scaly lesions with silvery scale | Atopic dermatitis, irritant dermatitis, cutaneous T-cell lymphoma, pityriasis rubra pilaris, seborrheic dermatitis | Localized: topical therapy with corticosteroids, calcipotriene (Dovonex), coal tars, anthralin (Anthra-Derm) or tazarotene (Tazorac). Generalized: phototherapy, systemic agents, combination therapy |
| Guttate psoriasis | Teardrop-shaped, pink to salmon, scaly plaques; usually on the trunk, with sparing of palms and soles | Pityriasis rosea, secondary syphilis, drug eruption | Ultraviolet B phototherapy, natural sunlight |
| Pustular psoriasis, localized | Erythematous papules or plaques studded with pustules; usually on palms or soles (palmoplantar pustular psoriasis) | Pustular drug eruption, dyshidrotic eczema, subcorneal pustular dermatosis | Same as for plaque-type psoriasis |
| Pustular psoriasis, generalized | Same as localized with a more general involvement; may be associated with systemic symptoms such as fever, malaise and diarrhea | Pustular drug eruption, subcorneal pustular dermatosis | Systemic therapy and/or hospitalization usually required |
| Erythrodermic psoriasis | Severe, intense, generalized erythema and scaling covering entire body; often associated with systemic symptoms; may or may not have had preexisting psoriasis | Drug eruption, eczematous dermatitis, mycosis fungoides, pityriasis rubra pilaris | Systemic therapy and/or hospitalization usually required |

**C.Calcipotriol**

**1.**Calcipotriol (Dovonex) has become an established therapy in psoriasis. Calcipotriol affects the growth of keratinocytes via its action at the level of vitamin D receptors. Calcipotriol is at least as effective as potent topical corticosteroids. Skin irritation is the main adverse effect. Topical calcipotriol may be used as an alternative to topical steroid therapy. Twice-daily application is indicated. Other than skin irritation, side effects are usually minimal; the risk of hypercalcemia is low. However, topical calcipotriol is more expensive than potent steroids.

**2.Tazarotene (Tazorac)** is a topical retinoid that appears to be safe and effective for the treatment of mild to moderate plaque psoriasis. Once-daily administration of tazarotene gel, 0.05 or 0.1 percent, compared favorably with topical fluocinonide.

**D.Methotrexate**

**1.**Methotrexate is usually administered in an intermittent low-dose regimen, such as once weekly. Administration can be oral, intravenous, intramuscular, or subcutaneous; the usual dose range is between 7.5 mg and 25 mg per week.

**2.**Folic acid, 1 mg daily, protects against some of the common side effects seen with low-dose MTX such as stomatitis. Monitoring for bone marrow suppression and hepatotoxicity are necessary.

**E.Retinoids.** Systemic retinoids (derivatives of Vitamin A) are indicated in patients with severe psoriasis. The retinoid of choice in psoriasis is acitretin (Soriatane). The usual dose of acitretin is 50 mg daily. Monitoring for

hypertriglyceridemia and hepatotoxicity are required with retinoid therapy. Side effects include cheilitis and alopecia. Acitretin is teratogenic and is only indicated in men and in women of nonreproductive potential.

**F.Cyclosporine** is effective in patients with severe psoriasis. Usual doses are in the range of 3 to 5 mg/kg per day orally. Improvement is generally observed within four weeks. Renal toxicity and hypertension are common.

**References:** See page 255.

# *Gynecologic Disorders*

## Management of the Abnormal Papanicolaou Smear

The Papanicolaou smear is a screening test for abnormalities that increases the risk of cervical cancer. Treatment decisions are based upon the results of colposcopically directed biopsies of the cervix. Papanicolaou smear reports are classified using the Bethesda System, which was revised in 2001.

**I.Pap Smear Report**

**Bethesda 2001 Pap Smear Report**

**Interpretation Result**
Negative for intraepithelial lesion or malignancy (when there is no cellular evidence of neoplasia, state this in the General Categorization above and/or in the Interpretation/Result section of the report, whether there are organisms or other non-neoplastic findings)

**Infection** (Trichomonas vaginalis, Candida spp., shift in flora suggestive of bacterial vaginosis, Actinomyces spp., cellular changes consistent with Herpes simplex virus)

**Other Non-neoplastic Findings (Optional to report; list not inclusive):**
- Reactive cellular changes associated with inflammation (includes typical repair) radiation, intrauterine contraceptive device (IUD)
- Glandular cells status post-hysterectomy
- Atrophy

**Other**
- Endometrial cells (in a woman ≥40 years of age) (specify if "negative for squamous intraepithelial lesion")

**Epithelial Cell Abnormalities**

**Squamous Cell**
- Atypical squamous cells
  - -of undetermined significance (ASC-US)
  - -cannot exclude HSIL (ASC-H)
- Low-grade squamous intraepithelial lesion (LSIL) encompassing: HPV/mild dysplasia/CIN 1
- High-grade squamous intraepithelial lesion (HSIL) encompassing: moderate and severe dysplasia, CIS/CIN 2 and CIN 3 with features suspicious for invasion (if invasion is suspected)
- Squamous cell carcinoma

**Glandular Cell**
- Atypical
  - -Endocervical cells (not otherwise specified or specify in comments)
  - -Glandular Cell (not otherwise specified or specify in comments)
  - -Endometrial cells (not otherwise specified or specify in comments)
  - -Glandular cells (not otherwise specified or specify in comments)
- Atypical
  - -Endocervical cells, favor neoplastic
  - -Glandular cells, favor neoplastic
- Endocervical adenocarcinoma in situ
- Adenocarcinoma (endocervical, endometrial, extrauterine, not otherwise specified (not otherwise specified)

**Other Malignant Neoplasms (specify)**

**II.Screening for cervical cancer**

**A.**Regular Pap smears are recommended for all women who are or have been sexually active and who have a cervix.

**B.**Testing should begin when the woman first engages in sexual intercourse. Adolescents whose sexual history is thought to be unreliable should be presumed to be sexually active at age 18.

**C.Screening recommendations.** The American Cancer Society, supported by the American College of Obstetricians and Gynecologists (ACOG), made the following recommendations in 2002 for cervical cancer screening:

**1.Initiating Screening.** Cervical cancer screening should be started approximately three years after the onset of vaginal intercourse, but no later than age 21. However, if it is certain that intercourse has never occurred, the provider and patient may defer initiating cervical cancer screening since such women are at very low risk of cervical cancer.

**2.Screening interval.** Cervical screening should be performed annually if conventional cervical cytology smears (Pap) are used or every two years with liquid-based cytology tests. The screening interval can then be increased to every two to three years in women with three or more consecutive normal cytology results who are greater than or equal to 30 years old.

**3.Discontinuing screening.** Screening for cervical cancer can be stopped in most women who have had a total hysterectomy for benign disease and those who are age 70 or older.

**D.ThinPrep cytology** is as good or better than conventional technology in diagnosing intraepithelial lesions. The sensitivity for diagnosis of high-grade lesions is 95

percent. This technique can reduce the false-negative rate of a conventional Pap smear by 60 percent.

**1.Other advantages of the ThinPrep system include:** A single specimen may be used to test for HPV, chlamydia, and gonorrhea infection, in addition to cervical cytology. Reflex HPV testing is an option for evaluation of women with cytology showing atypical squamous cells of undetermined significance (ASC-US).

**III.Techniques used in evaluation of the abnormal pap smear**

**A.Colposcopy** allows examination of the lower genital tract to identify epithelial changes. Abnormal areas should be targeted for biopsy to determine a pathologic diagnosis.

**IV.Atypical squamous cells**

**A.Atypical squamous cells of undetermined significance (ASCUS)** is further divided into ASC-US, which are qualified as "of undetermined significance," and ASC-H, in which a high-grade squamous intraepithelial lesion (HSIL) cannot be excluded.

**B.**ASC requires further evaluation. This cytologic diagnosis is common and frequently associated with spontaneously resolving, self-limited disease. However, 5 to 17 percent of patients with ASC and 24 to 94 percent of those with ASC-H will have CIN II or III at biopsy.

**C.Women with ASC-US**

**1.Management of minimally abnormal cervical cytology smears (ASC-US):**

**a.**If liquid-based cytology is used, reflex testing for HPV should be performed, alternatively cocollection for HPV DNA testing can be done at the time of a conventional cervical cytology smear.

**b.**Colposcopy should performed if human papillomavirus testing is positive. Thirty to 60 percent of women with ASC will test positive for high-risk HPV types and require immediate colposcopy.

**2.**Patients with a positive high-risk type HPV DNA test should be evaluated by colposcopy; those with a negative test may be triaged to repeat cytologic evaluation in 12 months. Management of women who test positive for high-risk HPV types, but have no CIN consists of either 1) cytological testing repeated in six and 12 months with colposcopic evaluation of ASC-US or greater or 2) HPV testing repeated in 12 months with colposcopy if HPV results are positive.

**V.Special circumstances**

**A.When an infectious organism is identified**, the patient should be contacted to determine if she is symptomatic. Antibiotic therapy is indicated for symptomatic infection.

**B.Reactive changes due to inflammation** are usually not associated with an organism on the Pap smear. The Pap smear does not need to be repeated unless the patient is HIV positive, in which case it should be repeated in four to six months.

**C.Atrophic epithelium** is a normal finding in postmenopausal women.

**1.**Administration of estrogen causes atypical atrophic, but not dysplastic, epithelium to mature into normal squamous epithelium.

**2.**Hormonal therapy given for vaginal atrophy should be followed by repeat cervical cytology one week after completing treatment. If negative, cytology should be repeated again in four to six months. If both tests are negative, the woman can return to routine screening intervals, but if either test is positive for ASC-US or greater, she should be evaluated with colposcopy.

**D.Immunosuppressed women**, including all women who are HIV positive, with ASC-US should be referred for immediate colposcopy, instead of HPV testing.

**E.ASC-US with absence of CIN on biopsy**. If colposcopic examination does not show CIN, then follow-up cytological testing should be performed in 12 months.

**F.ASC-US with biopsy proven CIN.** Since spontaneous regression is observed in approximately 60 percent of CIN I, expectant management with serial cytologic smears at three to four month intervals is reasonable for the reliable patient.

**G.Women with ASC-H**. All women with ASC-H on cytological examination should receive colposcopy. If repeat of cytology confirms ASC-H but biopsy is negative for CIN, follow-up cytology in six and 12 months or HPV DNA testing in 12 months is recommended. Colposcopy should be repeated for ASC or greater on cytology or a positive test for high risk HPV DNA. Biopsy proven CIN is treated, as appropriate.

**VI.Low- and high-grade intraepithelial neoplasia**

**A.Low-grade squamous intraepithelial lesions (LSIL)** may also be referred to as CIN I or mild dysplasia. Immediate referral for colposcopy is the recommended management for LSIL. Endocervical sampling should be done in nonpregnant women in whom the transformation zone cannot be fully visualized or a lesion extends into the endocervical canal. Endocervical sampling also should be done in nonpregnant women when no lesion is identified on colposcopy.

**1.**If no CIN is identified following satisfactory or unsatisfactory colposcopy and biopsies, then options for follow-up include either:

**a.**Repeat cytology testing at six and 12 months, or

**b.**HPV DNA testing at 12 months

**2.**Referral for repeat colposcopy is required if cytology yields ASC or greater or HPV DNA is positive for a high-risk type.

**3.**Women with histologically confirmed CIN I LSIL may be treated with ablation or excision or followed with

serial cytologic smears every three to six months if the entire lesion and limits of the transformation zone are completely visualized. LSIL confined to the endocervical canal may be followed with repeat smears obtained with a cytobrush and with ECC.

**4.Postmenopausal women.** Postmenopausal women may be managed by serial cytology at six and 12 months or HPV DNA testing at 12 months with referral to colposcopy for positive results. Women with atrophy are treated with intravaginal estrogen followed by repeat cytology seven days after completion of therapy, with referral to colposcopy if an abnormality persists. If repeat cytology is normal, then another cytology test should be obtained in four to six months. The woman can return to routine surveillance if both tests are normal, but should be referred for colposcopy if either test is positive.

**5.Adolescents**. Initial colposcopy may be deferred in adolescents. Instead, they may be managed with serial cytology at six and 12 months or HPV DNA testing at 12 months with referral to colposcopy for positive results.

**6.Pregnant women.** Colposcopy should be performed, with biopsy and endocervical curettage performed for any lesion suspicious for HSIL or more severe disease.

**B.High-grade squamous intraepithelial lesions**

**1.**A high-grade squamous intraepithelial lesion (HSIL) may also be referred to as CIN II or III, severe dysplasia, or carcinoma in situ (CIS). One to two percent of women with HSIL on a cytologic smear have invasive cancer at the time of further evaluation and 20 percent of women with biopsy-proven CIS will develop an invasive cancer if left untreated. All women with HSIL should be referred for colposcopy and endocervical sampling.

**C.Follow-up evaluation.** Pap smears are recommended every three to four months for the first year after treatment for dysplasia. Women with cervical dysplasia present at the LEEP or cone margin or in the concomitant ECC also need a follow-up colposcopy with endocervical curettage every six months for one year. Routine surveillance can be resumed if there is no recurrence after the first year. Surveillance consists of Pap smears on a yearly basis for most women, and on a twice-yearly basis for high-risk women (ie, HIV positive).

**VII.Abnormal glandular cells**

**A.**A report of atypical glandular cells (AGC) indicates the presence of glandular cells that could be coming from the endocervical or endometrial region. The Bethesda 2001 system classifies AGC into two subcategories:

**1.**AGC endocervical, endometrial, or not otherwise specified (NOS)

**2.**AGC favor neoplasia, endocervical or NOS

**B.**Additional categories for glandular cell abnormalities are:

**1.**Endocervical adenocarcinoma in situ (AIS)

**2.**Adenocarcinoma

**C.Evaluation of AGC or AIS on cervical cytology:** These women should be referred for colposcopy and sampling of the endocervical canal. Women over age 35 and younger women with AGC and unexplained vaginal bleeding also need an endometrial biopsy. Women with only atypical endometrial cells on cytology can be initially evaluated with endometrial biopsy.

**D.Endometrial cells in women ≥40 years of age:** Endometrial biopsy should be performed.

**References:** See page 255.

# Contraception

Approximately 31 percent of births are unintended; about 22 percent were "mistimed," while 9 percent were "unwanted."

**I.Sterilization**

**A.**Sterilization is the most common and effective form of contraception. While tubal ligation and vasectomy may be reversible, these procedures should be considered permanent.

**B.Essure microinsert sterilization device** is a permanent, hysteroscopic, tubal sterilization device which is 99.9 percent effective. The coil-like device is inserted in the office under local anesthesia into the fallopian tubes where it is incorporated by tissue. After placement, women use alternative contraception for three months, after which hysterosalpingography is performed to assure correct placement. Postoperative discomfort is minimal.

**C.Tubal ligation** is usually performed as a laparoscopic procedure in outpatients or in postpartum women in the hospital. The techniques used are unipolar or bipolar coagulation, silicone rubber band or spring clip application, and partial salpingectomy.

**D.Vasectomy** (ligation of the vas deferens) can be performed in the office under local anesthesia. A semen analysis should be done three to six months after the procedure to confirm azoospermia.

**II.Oral contraceptives**

**A.**Combined (estrogen-progestin) oral contraceptives are reliable, and they have noncontraceptive benefits, which include reduction in dysmenorrhea, iron deficiency, ovarian cancer, endometrial cancer.

| Combination Oral Contraceptives | | |
|---|---|---|
| **Drug** | **Progestin, mg** | **Estrogen** |
| **Monophasic combinations** | | |
| Ortho-Novum 1 /35 21, 28 | Norethindrone (1) | Ethinyl estradiol (35) |
| Ovcon 35 21, 28 | Norethindrone (0.4) | Ethinyl estradiol (35) |
| Brevicon 21, 28 | Norethindrone (0.5) | Ethinyl estradiol (35) |
| Modicon 28 | Norethindrone (0.5) | Ethinyl estradiol (35) |
| Necon 0.5/35E 21, 28 | Norethindrone (0.5) | Ethinyl estradiol (35) |
| Nortrel 0.5/35 28 | Norethindrone (0.5) | Ethinyl estradiol (35) |
| Necon 1 /35 21, 28 | Norethindrone (1) | Ethinyl estradiol (35) |
| Norinyl 1 /35 21, 28 | Norethindrone (1) | Ethinyl estradiol (35) |
| Nortrel 1 /35 21, 28 | Norethindrone (1) | Ethinyl estradiol (35) |
| Loestrin 1 /20 21, 28 | Norethindrone acetate (1) | Ethinyl estradiol (20) |
| Microgestin 1 /20 28 | Norethindrone acetate (1) | Ethinyl estradiol (20) |
| Loestrin 1.5/30 21, 28 | Norethindrone acetate (1.5) | Ethinyl estradiol (30) |
| Microgestin 1.5/30 28 | Norethindrone acetate (1.5) | Ethinyl estradiol (30) |
| Alesse 21, 28 | Levonorgestrel (0.1) | Ethinyl estradiol (20) |
| Aviane 21, 28 | Levonorgestrel (0.1) | Ethinyl estradiol (20) |
| Lessina 28 | Levonorgestrel (0.1) | Ethinyl estradiol (20) |
| Levlite 28 | Levonorgestrel (0.1) | Ethinyl estradiol (20) |
| Necon 1/50 21, 28 | Norethindrone (1) | Mestranol (50) |
| Norinyl 1150 21, 28 | Norethindrone (1) | Mestranol (50) |
| Ortho-Novum 1/50 28 | Norethindrone (1) | Mestranol (50) |
| Ovcon 50 28 | Norethindrone (1) | Ethinyl estradiol (50) |
| Cyclessa 28 | Desogestrel (0.1) | Ethinyl estradiol (25) |
| Apri 28 | Desogestrel (0.15) | Ethinyl estradiol (30) |
| Desogen 28 | Desogestrel (0.15) | Ethinyl estradiol (30) |
| Ortho-Cept 21, 28 | Desogestrel (0.15) | Ethinyl estradiol (30) |
| Yasmin 28 | Drospirenone (3) | Ethinyl estradiol (30) |
| Demulen 1 /35 21, 28 | Ethynodiol diacetate (1) | Ethinyl estradiol (35) |
| Zovia 1 /35 21, 28 | Ethynodiol diacetate (1) | Ethinyl estradiol (35) |
| Demulen 1/50 21, 28 | Ethynodiol diacetate (1) | Ethinyl estradiol (50) |
| Zovia 1 /50 21, 28 | Ethynodiol diacetate (1) | Ethinyl estradiol (50) |
| Levlen 21, 28 | Levonorgestrel (0.15) | Ethinyl estradiol (30) |
| Levora 21, 28 | Levonorgestrel (0.15) | Ethinyl estradiol (30) |
| Nordette 21, 28 | Levonorgestrel (0.15) | Ethinyl estradiol (30) |
| Ortho-Cyclen 21, 28 | Norgestimate (0.25) | Ethinyl estradiol (35) |
| Lo/Ovral 21, 28 | Norgestrel (0.3) | Ethinyl estradiol |

| Drug | Progestin, mg | Estrogen |
|---|---|---|
| | | (30) |
| Low-Ogestrel 21, 28 | Norgestrel (0.3) | Ethinyl estradiol (30) |
| Ogestrel 28 | Norgestrel (0.5) | Ethinyl estradiol (50) |
| Ovral 21, 28 | Norgestrel (0.5) | Ethinyl estradiol (50) |
| Seasonale | Levonorgestrel (0.15) | Ethinyl estradiol (0.03) |
| **Multiphasic Combinations** | | |
| Kariva 28 | Desogestrel (0.15) | Ethinyl estradiol (20, 0, 10) |
| Mircette 28 | Desogestrel (0.15) | Ethinyl estradiol (20, 0, 10) |
| Tri-Levlen 21, 28 | Levonorgestrel (0.05, 0.075, 0.125) | Ethinyl estradiol (30, 40, 30) |
| Triphasil 21, 28 | Levonorgestrel (0.05, 0.075, 0.125) | Ethinyl estradiol (30, 40, 30) |
| Trivora 28 | Levonorgestrel (0.05, 0.075, 0.125) | Ethinyl estradiol (30, 40, 30) |
| Necon 10/11 21, 28 | Norethindrone (0.5, 1) | Ethinyl estradiol (35) |
| Ortho-Novum 10/11 28 | Norethindrone (0.5, 1) | Ethinyl estradiol (35) |
| Ortho-Novum 7/7/7 21, 28 | Norethindrone (0.5, 0.75, 1) | Ethinyl estradiol (35) |
| Tri-Norinyl 21, 28 | Norethindrone (0.5, 1, 0.5) | Ethinyl estradiol (35) |
| Estrostep 28 | Norethindrone acetate (1) | Ethinyl estradiol (20, 30, 35) |
| Ortho Tri-Cyclen 21, 28 | Norgestimate (0.18, 0.215, 0.25) | Ethinyl estradiol (35) |

**B.Pharmacology**

**1.**Ethinyl estradiol is the estrogen in virtually all OCs.

**2.**Commonly used progestins include norethindrone, norethindrone acetate, and levonorgestrel. Ethynodiol diacetate is a progestin, which also has significant estrogenic activity. New progestins have been developed with less androgenic activity; however, these agents may be associated with deep vein thrombosis.

**C.Mechanisms of action**

**1.**The most important mechanism of action is estrogen-induced inhibition of the midcycle surge of gonadotropin secretion, so that ovulation does not occur.

**2.**Another potential mechanism of contraceptive action is suppression of gonadotropin secretion during the follicular phase of the cycle, thereby preventing follicular maturation.

**3.**Progestin-related mechanisms also may contribute to the contraceptive effect. These include rendering the endometrium is less suitable for implantation and making the cervical mucus less permeable to penetration by sperm.

**D.Contraindications**

**1.Absolute contraindications to OCs:**

**a.**Previous thromboembolic event or stroke
**b.**History of an estrogen-dependent tumor
**c.**Active liver disease
**d.**Pregnancy
**e.**Undiagnosed abnormal uterine bleeding
**f.**Hypertriglyceridemia
**g.**Women over age 35 years who smoke heavily (greater than 15 cigarettes per day)

**2.Screening requirements.** Hormonal contraception can be safely provided after a careful medical history and blood pressure measurement. Pap smears are not required before a prescription for OCs.

**E.Efficacy**. When taken properly, OCs are a very effective form of contraception. The actual failure rate is 2 to 3 percent due primarily to missed pills or failure to resume therapy after the seven-day pill-free interval.

| Noncontraceptive Benefits of Oral Contraceptive Pills | |
|---|---|
| Dysmenorrhea<br>Mittelschmerz<br>Metrorrhagia<br>Premenstrual syndrome<br>Hirsutism<br>Ovarian and endometrial cancer | Functional ovarian cysts<br>Benign breast cysts<br>Ectopic pregnancy<br>Acne<br>Endometriosis |

**F.Drug interactions.** The metabolism of OCs is accelerated by phenobarbital, phenytoin and rifampin. The contraceptive efficacy of an OC is likely to be decreased

in women taking these drugs. Other antibiotics (with the exception of rifampin) do not affect the pharmacokinetics of ethinyl estradiol.

**G.Preparations**

**1.**There are two types of oral contraceptive pills: combination pills that contain both estrogen and progestin, and the progestin-only pill ("mini-pill"). Progestin-only pills, which are associated with more breakthrough bleeding than combination pills, are rarely prescribed except in lactating women. Combination pills are packaged in 21-day or 28-day cycles. The last seven pills of a 28-day pack are placebo pills.

**2.**Monophasic combination pills contain the same dose of estrogen and progestin in each of the 21 hormonally active pills. Current pills contain on average 30 to 35 µg. Pills containing less than 50 µg of ethinyl estradiol are "low-dose" pills.

**3.20 µg preparations.** Several preparations containing only 20 µg of ethinyl estradiol are now available (Lo-Estrin 1/20, Mircette, Alesse, Aviane). These are often used for perimenopausal women who want contraception with the lowest estrogen dose possible. These preparations provide enough estrogen to relieve vasomotor flashes. Perimenopausal women often experience hot flashes and premenstrual mood disturbances during the seven-day pill-free interval. Mircette, contains 10 µg of ethinyl estradiol on five of the seven "placebo" days, which reduces flashes and mood symptoms.

**4.Seasonale** is a 91-day oral contraceptive. Tablets containing the active hormones are taken for 12 weeks (84 days), followed by 1 week (7 days) of placebo tablets. Seasonale contains levonorgestrel (0.15 mg) and ethinyl estradiol (0.03 mg). Many women, especially in the first few cycles, have more spotting between menstrual periods. Seasonale is as effective and safe as traditional birth control pills.

**5.Yasmin** contains 30 mcg of ethinyl estradiol and drospirenone. Drospirenone has anti-mineralocorticoid activity. It can help prevent bloating, weight gain, and hypertension, but it can increase serum potassium. Yasmin is contraindicated in patients at risk for hyperkalemia due to renal, hepatic, or adrenal disease. Yasmin should not be combined with other drugs that can increase potassium, such as ACE inhibitors, angiotensin receptor blockers, potassium-sparing diuretics, potassium supplements, NSAIDs, or salt substitutes.

**6.Third-generation progestins**

**a.**More selective progestins include norgestimate, desogestrel, and gestodene. They have some structural modifications that lower their androgen activity. Norgestimate (eg, Ortho-Cyclen or Tri-Cyclen) and desogestrel (eg, Desogen or Ortho-Cept) are the least androgenic compounds in this class. The new progestins are not much less androgenic than norethindrone.

**b.**The newer OCs are more effective in reducing acne and hirsutism in hyperandrogenic women. They are therefore an option for women who have difficulty tolerating older OCs. There is an increased risk of deep venous thrombosis with the use of these agents, and they should not be routinely used.

**H.Recommendations**

**1.**Monophasic OCs containing the second generation progestin, norethindrone (Ovcon 35, Ortho-Novum 1/35) are recommended when starting a patient on OCs for the first time. This progestin has very low androgenicity when compared to other second generation progestins, and also compares favorably to the third generation progestins in androgenicity.

**2.**The pill should be started on the first day of the period to provide the maximum contraceptive effect in the first cycle. However, most women start their pill on the first Sunday after the period starts. Some form of back-up contraception is needed for the first month if one chooses the Sunday start, because the full contraceptive effect might not be provided in the first pill pack.

**Factors to Consider in Starting or Switching Oral Contraceptive Pills**

| Objective | Action | Products that achieve the objective |
|---|---|---|
| To minimize high risk of thrombosis | Select a product with a lower dosage of estrogen. | Alesse, Aviane, Loestrin 1/20, Levlite, Mircette |
| To minimize nausea, breast tenderness or vascular headaches | Select a product with a lower dosage of estrogen. | Alesse, Aviane, Levlite, Loestrin 1/20, Mircette |
| To minimize spotting or breakthrough bleeding | Select a product with a higher dosage of estrogen or a progestin with greater potency. | Lo/Ovral, Nordette, Ortho-Cept, Ortho-Cyclen, Ortho Tri-Cyclen |
| To minimize androgenic effects | Select a product containing a low-dose norethindrone or ethynodiol diacetate. | Brevicon, Demulen 1/35, Modicon, Ovcon 35 |

| Objective | Action | Products that achieve the objective |
|---|---|---|
| To avoid dyslipidemia | Select a product containing a low-dose norethindrone or ethynodiol diacetate. | Brevicon, Demulen 1/35, Modicon, Ovcon 35 |

**Instructions on the Use of Oral Contraceptive Pills**

**Initiation of use (choose one):**
The patient begins taking the pills on the first day of menstrual bleeding.
The patient begins taking the pills on the first Sunday after menstrual bleeding begins.
The patient begins taking the pills immediately if she is definitely not pregnant and has not had unprotected sex since her last menstrual period.

**Missed pill**
If it has been less than 24 hours since the last pill was taken, the patient takes a pill right away and then returns to normal pill-taking routine.
If it has been 24 hours since the last pill was taken, the patient takes both the missed pill and the next scheduled pill at the same time.
If it has been more than 24 hours since the last pill was taken (ie, two or more missed pills), the patient takes the last pill that was missed, throws out the other missed pills and takes the next pill on time. Additional contraception is used for the remainder of the cycle.

**Additional contraceptive method**
Use an additional contraceptive method for the first 7 days after initially starting oral contraceptive pills.
Use an additional contraceptive method for 7 days if more than 12 hours late in taking an oral contraceptive pill.
Use an additional contraceptive method while taking an interacting drug and for 7 days thereafter.

**III.Injectable contraceptives**

**A.Depot medroxyprogesterone acetate** (DMPA, Depo-Provera) is an injectable contraceptive. Deep intramuscular injection of 150 mg results in effective contraception for three to four months. Effectiveness is 99.7 percent.

**B.**Women who receive the first injection after the seventh day of the menstrual cycle should use a second method of contraception for seven days. The first injection should be administered within five days after the onset of menses, in which case alternative contraception is not necessary.

**C.**Ovulation is suppressed for at least 14 weeks after injection of a 150 mg dose of DMPA. Therefore, injections should repeated every three months. A pregnancy test must be administered to women who are more than two weeks late for an injection.

**D.**Return of fertility can be delayed for up to 18 months after cessation of DMPA. DMPA is not ideal for women who may wish to become pregnant soon after cessation of contraception.

**E.**Amenorrhea, irregular bleeding, and weight gain (typically 1 to 3 kg) are the most common adverse effects of DMPA. Adverse effects also include acne, headache, and depression. Fifty percent of women report amenorrhea by one year. Persistent bleeding may be treated with 50 µg of ethinyl estradiol for 14 days.

**F.Medroxyprogesterone acetate/estradiol cypionate (MPA/E2C, Lunelle)** is a combined (25 mg MPA and 5 mg E2C), injectable contraceptive.

**1.**Although monthly IM injections are required, MPA/E2C has several desirable features:

**a.**It has nearly 100 percent effectiveness in preventing pregnancy.

**b.**Fertility returns within three to four months after it is discontinued.

**c.**Irregular bleeding is less common than in women given MPA alone.

**2.**Weight gain, hypertension, headache, mastalgia, or other nonmenstrual complaints are common.

**3.**Lunelle should be considered for women who forget to take their birth control pills or those who want a discreet method of contraception. The initial injection should be given during the first 5 days of the menstrual cycle or within 7 days of stopping oral contraceptives. Lunelle injections should be given every 28 to 30 days; 33 days at the most.

**G.Transdermal contraceptive patch**

**1.Ortho Evra** is a transdermal contraceptive patch, which is as effective as oral contraceptives. Ortho Evra delivers 20 µg of ethinyl estradiol and 150 µg of norelgestromin daily for 6 to 13 months. Compliance is better with the patch. The patch is applied at the beginning of the menstrual cycle. A new patch is applied each week for 3 weeks; week 4 is patch-free. It is sold in packages of 3 patches. Effectiveness is similar to oral contraceptives.

**2.**Breakthrough bleeding during the first two cycles, dysmenorrhea, and breast discomfort are more common in women using the patch. A reaction at the site of application of the patch occurs in 1.9 percent of the women. Contraceptive efficacy may be slightly lower in women weighing more than 90 kg.

**H.Contraceptive vaginal ring (NuvaRing)** delivers 15 µg ethinyl estradiol and 120 µg of etonogestrel daily) and is worn intravaginally for three weeks of each four week cycle. Advantages of this method include avoidance of gastrointestinal metabolism, rapid return to ovulation after discontinuation, lower doses of hormones, ease and convenience, and improved cycle control.

**IV.Barrier methods**

**A.**Barrier methods of contraception, such as the condom, diaphragm, cervical cap, and spermicides, have fewer side effects than hormonal contraception.

**B.**The diaphragm and cervical cap require fitting by a clinician and are only effective when used with a spermicide. They must be left in the vagina for six to eight hours after intercourse; the diaphragm needs to be removed after this period of time, while the cervical cap can be left in place for up to 24 hours. These considerations have caused them to be less desirable methods of contraception. A major advantage of barrier contraceptives is their efficacy in protecting against sexually transmitted diseases and HIV infection.

**V.Intrauterine devices**

**A.**The currently available intrauterine devices (IUDs) are safe and effective methods of contraception:

**1.Copper T380 IUD** induces a foreign body reaction in the endometrium. It is effective for 8 to 10 years.

**2.Progesterone-releasing IUDs** inhibit sperm survival and implantation. They also decrease menstrual blood loss and relieve dysmenorrhea. **Paragard** is replaced every 10 years. **Progestasert** IUDs must be replaced after one year.

**3.Levonorgestrel IUD (Mirena)** provides effective contraception for five years.

**B.Infection**

**1.**Women who are at low risk for sexually transmitted diseases do not have a higher incidence of pelvic inflammatory disease with use of an IUD. An IUD should not be inserted in women at high risk for sexually transmitted infections, and women should be screened for the presence of sexually transmitted diseases before insertion.

**2.Contraindications to IUDs:**

**a.**Women at high risk for bacterial endocarditis (eg, rheumatic heart disease, prosthetic valves, or a history of endocarditis).

**b.**Women at high risk for infections, including those with AIDS and a history of intravenous drug use.

**c.**Women with uterine leiomyomas which alter the size or shape of the uterine cavity.

**VI.Lactation**

**A.**Women who breast-feed have a delay in resumption of ovulation postpartum. It is probably safest to resume contraceptive use in the third postpartum month for those who breast-feed full time, and in the third postpartum week for those who do not breast-feed.

**B.**A nonhormonal contraceptive or progesterone-containing hormonal contraceptive can be started at any time; an estrogen-containing oral contraceptive pill should not be started before the third week postpartum because women are still at increased risk of thromboembolism prior to this time. Oral contraceptive pills can decrease breast milk, while progesterone-containing contraceptives may increase breast milk.

**VII.Progestin-only agents**

**A.**Progestin-only agents are slightly less effective than combination oral contraceptives. They have failure rates of 0.5 percent compared with the 0.1 percent rate with combination oral contraceptives.

**B.**Progestin-only oral contraceptives (Micronor, Nor-QD, Ovrette) provide a useful alternative in women who cannot take estrogen. Progestin-only contraception is recommended for nursing mothers. Milk production is unaffected by use of progestin-only agents.

**C.**If the usual time of ingestion is delayed for more than three hours, an alternative form of birth control should be used for the following 48 hours. Because progestin-only agents are taken continuously, without hormone-free periods, menses may be irregular, infrequent or absent.

**VIII.Postcoital contraception**

**A.**Emergency postcoital contraception consists of administration of drugs within 72 hours to women who have had unprotected intercourse (including sexual assault), or to those who have had a failure of another method of contraception (eg, broken condom).

**B.Preparations**

**1.**Menstrual bleeding typically occurs within three days after administration of most forms of hormonal postcoital contraception. A pregnancy test should be performed if bleeding has not occurred within four weeks.

**2.Preven Emergency Contraceptive Kit** includes four combination tablets, each containing 50 µg of ethinyl estradiol and 0.25 mg of levonorgestrel, and a pregnancy test to rule out pregnancy before taking the tablets. Instructions are to take two of the tablets as soon as possible within 72 hours of coitus, and the other two tablets twelve hours later.

**3.**An oral contraceptive such as Ovral (two tablets twelve hours apart) or Lo/Ovral (4 tablets twelve hours apart) can also be used.

**4.**Nausea and vomiting are the major side effects. Meclizine 50 mg, taken one hour before the first dose, reduces nausea and vomiting but can cause some sedation.

**5.Plan B** is a pill pack that contains two 0.75 mg tablets of levonorgestrel to be taken twelve hours apart. The cost is comparable to the Preven kit ($20). This regimen may be more effective and better tolerated than an estrogen-progestin regimen.

**6.Copper T380 IUD.** A copper intrauterine device (IUD) placed within 120 hours of unprotected intercourse can also be used as a form of emergency contraception. An advantage of this method is that it provides continuing contraception after the initial event.

**Emergency Contraception**

1. Consider pretreatment one hour before each oral contraceptive pill dose, using one of the following orally administered antiemetic agents:
   Prochlorperazine (Compazine), 5 to 10 mg
   Promethazine (Phenergan), 12.5 to 25 mg
   Trimethobenzamide (Tigan), 250 mg
   Meclizine (Antivert) 50 mg
2. Administer the first dose of oral contraceptive pill within 72 hours of unprotected coitus, and administer the second dose 12 hours after the first dose. Brand name options for emergency contraception include the following:
   **Preven Kit** – two pills per dose (0.5 mg of levonorgestrel and 100 µg of ethinyl estradiol per dose)
   **Plan B** – one pill per dose (0.75 mg of levonorgestrel per dose)
   **Ovral** – two pills per dose (0.5 mg of levonorgestrel and 100 µg of ethinyl estradiol per dose)
   **Nordette** – four pills per dose (0.6 mg of levonorgestrel and 120 µg of ethinyl estradiol per dose)
   **Triphasil** – four pills per dose (0.5 mg of levonorgestrel and 120 µg of ethinyl estradiol per dose)

**References:** See page 255.

# Endometriosis

Endometriosis is characterized by the presence of endometrial tissue on the ovaries, fallopian tubes or other abnormal sites, causing pain or infertility. Women are usually 25 to 29 years old at the time of diagnosis. Approximately 24 percent of women who complain of pelvic pain are subsequently found to have endometriosis. The overall prevalence of endometriosis is estimated to be 5 to 10 percent.

**I.Clinical evaluation**

**A.**Endometriosis should be considered in any woman of reproductive age who has pelvic pain. The most common symptoms are dysmenorrhea, dyspareunia, and low back pain that worsens during menses. Rectal pain and painful defecation may also occur. Other causes of secondary dysmenorrhea and chronic pelvic pain (eg, upper genital tract infections, adenomyosis, adhesions) may produce similar symptoms.

**Differential Diagnosis of Endometriosis**

**Generalized pelvic pain**
- Pelvic inflammatory disease
- Endometritis
- Pelvic adhesions
- Neoplasms, benign or malignant
- Ovarian torsion
- Sexual or physical abuse
- Nongynecologic causes

**Dysmenorrhea**
- Primary
- Secondary (adenomyosis, myomas, infection, cervical stenosis)

**Dyspareunia**
- Musculoskeletal causes (pelvic relaxation, levator spasm)
- Gastrointestinal tract (constipation, irritable bowel syndrome)
- Urinary tract (urethral syndrome, interstitial cystitis)
- Infection
- Pelvic vascular congestion
- Diminished lubrication or vaginal expansion because of insufficient arousal

**Infertility**
- Male factor
- Tubal disease (infection)
- Anovulation
- Cervical factors (mucus, sperm antibodies, stenosis)
- Luteal phase deficiency

**B.**Infertility may be the presenting complaint for endometriosis. Infertile patients often have no painful symptoms.

**C.Physical examination.** The physician should palpate for a fixed, retroverted uterus, adnexal and uterine tenderness, pelvic masses or nodularity along the uterosacral ligaments. A rectovaginal examination should identify uterosacral, cul-de-sac or septal nodules. Most women with endometriosis have normal pelvic findings.

**II.Treatment**

**A.**Confirmatory laparoscopy is usually required before treatment is instituted. In women with few symptoms, an empiric trial of oral contraceptives or progestins may be warranted to assess pain relief.

**B.Medical treatment**

**1.**Initial therapy also should include a nonsteroidal anti-inflammatory drug.

**a.**Naproxen (Naprosyn) 500 mg followed by 250 mg PO tid-qid prn [250, 375,500 mg].

**b.**Naproxen sodium (Aleve) 200 mg PO tid prn.

**c.**Naproxen sodium (Anaprox) 550 mg, followed by 275 mg PO tid-qid prn.

**d.**Ibuprofen (Motrin) 800 mg, then 400 mg PO q4-6h prn.

**e.**Mefenamic acid (Ponstel) 500 mg PO followed by 250 mg q6h prn.

**2.Progestational agents.** Progestins are similar to combination OCPs in their effects on FSH, LH and endometrial tissue. They may be associated with more bothersome adverse effects than OCPs. Progestins are effective in reducing the symptoms of endometriosis. Oral progestin regimens may include once-daily administration of medroxyprogesterone at the lowest effective dosage (5 to 20 mg). Depot medroxyprogesterone may be given intramuscularly every two weeks for two months at 100 mg per dose and then once a month for four months at 200 mg per dose.

**3.Oral contraceptive pills (OCPs)** suppress LH and FSH and prevent ovulation. Combination OCPs alleviate symptoms in about three quarters of patients. Oral contraceptives can be taken continuously (with no placebos) or cyclically, with a week of placebo pills between cycles. The OCPs can be discontinued after six months or continued indefinitely.

**4.Danazol (Danocrine)** has been highly effective in relieving the symptoms of endometriosis, but adverse effects may preclude its use. Adverse effects include headache, flushing, sweating and atrophic vaginitis. Androgenic side effects include acne, edema, hirsutism, deepening of the voice and weight gain. The initial dosage should be 800 mg per day, given in two divided oral doses. The overall response rate is 84 to 92 percent.

**Medical Treatment of Endometriosis**

| Drug | Dosage | Adverse effects |
|---|---|---|
| Danazol (Danocrine) | 800 mg per day in 2 divided doses | Estrogen deficiency, androgenic side effects |
| Oral contraceptives | 1 pill per day (continuous or cyclic) | Headache, nausea, hypertension |
| Medroxyprogesterone (Provera) | 5 to 20 mg orally per day | Same as with other oral progestins |
| Medroxyprogesterone suspension (Depo-Provera) | 100 mg IM every 2 weeks for 2 months; then 200 mg IM every month for 4 months or 150 mg IM every 3 months | Weight gain, depression, irregular menses or amenorrhea |
| Norethindrone (Aygestin) | 5 mg per day orally for 2 weeks; then increase by 2.5 mg per day every 2 weeks up to 15 mg per day | Same as with other oral progestins |
| Leuprolide (Lupron) | 3.75 mg IM every month for 6 months | Decrease in bone density, estrogen deficiency |
| Goserelin (Zoladex) | 3.6 mg SC (in upper abdominal wall) every 28 days | Estrogen deficiency |
| Nafarelin (Synarel) | 400 mg per day: 1 spray in 1 nostril in a.m.; 1 spray in other nostril in p.m.; start treatment on day 2 to 4 of menstrual cycle | Estrogen deficiency, bone density changes, nasal irritation |

**C.GnRH agonists.** These agents (eg, leuprolide [Lupron], goserelin [Zoladex]) inhibit the secretion of gonadotropin. GnRH agonists are contraindicated in pregnancy and have hypoestrogenic side effects. They produce a mild degree of bone loss. Because of concerns about osteopenia, "add-back" therapy with low-dose estrogen has been recommended. The dosage of leuprolide is a single monthly 3.75-mg depot injection given intramuscularly. Goserelin, in a dosage of 3.6 mg, is administered subcutaneously every 28 days. A nasal spray (nafarelin [Synarel]) may be used twice daily. The response rate is similar to that with danazol; about 90 percent of patients experience pain relief.

**D.Surgical treatment**

**1.**Surgical treatment is the preferred approach to infertile patients with advanced endometriosis. Laparoscopic ablation of endometriosis lesions may result in a 13 percent increase in the probability of pregnancy.

**2.**Definitive surgery, which includes hysterectomy and oophorectomy, is reserved for women with intractable pain who no longer desire pregnancy.

**References:** See page 255.

# Premenstrual Syndrome and Premenstrual Dysphoric Disorder

Premenstrual syndrome (PMS) is characterized by physical and behavioral symptoms that occur repetitively in the second half of the menstrual cycle and interfere with some aspects of the woman's life. Premenstrual dysphoric disorder (PMDD) is the most severe form of PMS, with the prominence anger, irritability, and internal tension. PMS affects up to 75 percent of women with regular menstrual cycles, while PMDD affects only 3 to 8 percent of women.

**I.Symptoms**

**A.**The most common physical manifestation of PMS is abdominal bloating, which occurs in 90 percent of women with this disorder; breast tenderness and headaches are also common, occurring in more than 50 percent of cases.

**B.**The most common behavioral symptom of PMS is an extreme sense of fatigue which is seen in more than 90 percent. Other frequent behavioral complaints include irritability, tension, depressed mood, labile mood (80 percent), increased appetite (70 percent), and forgetfulness and difficulty concentrating (50 percent).

**C.**Other common findings include acne, oversensitivity to environmental stimuli, anger, easy crying, and gastrointestinal upset. Hot flashes, heart palpitations, and dizziness occur in 15 to 20 percent of patients. Symptoms should occur in the luteal phase only.

**Symptom Clusters Commonly Noted in Patients with PMS**

| | |
|---|---|
| **Affective Symptoms** | **Cognitive or performance** |
| Depression or sadness | Mood instability or mood swings |
| Irritability | Difficulty in concentrating |
| Tension | Decreased efficiency |
| Anxiety | Confusion |
| Tearfulness or crying easily | Forgetfulness |
| Restlessness or jitteriness | Accident-prone |
| Anger | Social avoidance |
| Loneliness | Temper outbursts |
| Appetite change | Energetic |
| Food cravings | **Fluid retention** |
| Changes in sexual interest | Breast tenderness or swelling |
| Pain | Weight gain |
| Headache or migraine | Abdominal bloating or swelling |
| Back pain | Swelling of extremities |
| Breast pain | **General somatic** |
| Abdominal cramps | Fatigue or tiredness |
| General or muscular pain | Dizziness or vertigo |
| | Nausea |
| | Insomnia |

**UCSD Criteria for Premenstrual Syndrome**

At least one of the following affective and somatic symptoms during the five days before menses in each of the three previous cycles:
**Affective symptoms:** depression, angry outbursts, irritability, anxiety, confusion, social withdrawal
**Somatic symptoms:** breast tenderness, abdominal bloating, headache, swelling of extremities Symptoms relieved from days 4 through 13 of the menstrual cycle

**DSM-IV Criteria for Premenstrual Dysphoric Disorder**

- Five or more symptoms
- At least one of the following four symptoms:
  - Markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts
  - Marked anxiety, tension, feeling of being "keyed up" or "on edge"
  - Marked affective lability
  - Persistent and marked anger or irritability or increase in interpersonal conflicts
- Additional symptoms that may be used to fulfill the criteria:
  - Decreased interest in usual activities
  - Subjective sense of difficulty in concentrating
  - Lethargy, easy fatigability, or marked lack of energy
  - Marked change in appetite, overeating, or specific food cravings
  - Hypersomnia or insomnia
  - Subjective sense of being overwhelmed or out of control
- Other physical symptoms such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of bloating, or weight gain
- Symptoms occurring during last week of luteal phase
- Symptoms are absent postmenstrually
- Disturbances that interfere with work or school or with usual social activities and relationships
- Disturbances that are not an exacerbation of symptoms of another disorder

**Differential Diagnosis of Premenstrual Syndrome**

| | |
|---|---|
| Affective disorder (eg, depression, anxiety, dysthymia, panic) | Endometriosis |
| Anemia | Hypothyroidism |
| Anorexia or bulimia | Oral contraceptive pill use |
| Chronic medical conditions (eg, diabetes mellitus) | Perimenopause |
| Dysmenorrhea | Personality disorder |
| | Substance abuse disorders |

**D.Differential diagnosis**

**1.**PMDD should be differentiated from premenstrual exacerbation of an underlying major psychiatric disorder, as well as medical conditions such as hyper- or hypothyroidism.

**2.**About 13 percent of women with PMS are found to have a psychiatric disorder alone with no evidence of PMS, while 38 percent had premenstrual exacerbation of underlying depressive and anxiety disorders.

**3.**39 percent of women with PMDD meet criteria for mood or anxiety disorders.

**4.**The assessment of patients with possible PMS or PMDD should begin with the history, physical examination, chemistry profile, complete blood count, and serum TSH. The history should focus in particular on the regularity of menstrual cycles. Appropriate gynecologic endocrine evaluation should be performed if the cycles are irregular (lengths less than 25 or greater than 36 days).

**5.**The patient should be asked to record symptoms prospectively for two months. If the patient fails to demonstrate a symptom free interval in the follicular phase, she should be evaluated for a mood or anxiety disorder.

**II.Nonpharmacologic therapy**

**A.**Relaxation therapy and cognitive behavioral therapy have shown some benefit. Behavioral measures include keeping a symptom diary, getting adequate rest and exercise, and making dietary changes.

**B.**Sleep disturbances, ranging from insomnia to excessive sleep, are common. A structured sleep schedule with consistent sleep and wake times is recommended. Sodium restriction may minimize bloating, fluid retention, and breast swelling and tenderness. Caffeine restriction and aerobic exercise often reduce symptoms.

**III.Dietary Supplementation**

**A.**Vitamin E supplementation is a treatment for mastalgia. The administration of 400 IU per day of vitamin E during the luteal phase improves affective and somatic symptoms.

**B.**Calcium carbonate in a dosage of 1200 mg per day for three menstrual cycles results in symptom improvement in 48 percent of women with PMS.

**IV.Pharmacologic Therapy**

**A.**Fluoxetine (Sarafem) and sertraline (Zoloft) have been approved for the treatment of PMDD. SSRIs are recommended as initial drug therapy in women with PMS and PMDD. Common side effects of SSRIs include insomnia, drowsiness, fatigue, nausea, nervousness, headache, mild tremor, and sexual dysfunction.

**B.**Fluoxetine (Sarafem) 20 mg or sertraline (Zoloft) 50 mg, taken in the morning, is best tolerated and sufficient to improve symptoms. Fluoxetine or sertraline can be given during the 14 days before the menstrual period.

**C.**Benefit has also been demonstrated for citalopram (Celexa) during the 14 days before the menstrual period.

**Prescription Medications Commonly Used in the Treatment of Premenstrual Syndrome (PMS)**

| Drug class and representative agents | Dosage | Recommendations | Side effects |
|---|---|---|---|
| **SSRIs** | | | |
| Fluoxetine (Sarafem) | 10 to 20 mg per day | First-choice agents for the treatment of PMDD. Effective in alleviating behavioral and physical symptoms of PMS and PMDDtion Administer during luteal phase (14 days before menses). | Insomnia, drowsiness, fatigue, nausea, nervousness, headache, mild tremor, sexual dysfunc- |
| Sertraline (Zoloft) | 50 to 150 mg per day | | |
| Paroxetine (Paxil) | 10 to 30 mg per day | | |
| Fluvoxamine (Luvox) | 25 to 50 mg per day | | |
| Citalopram (Celexa) | 20 to 40 mg per day | | |
| **Diuretics** | | | |
| Spironolactone (Aldactone) | 25 to 100 mg per day luteal phase | Effective in alleviating breast tenderness and bloating. | Antiestrogenic effects, hyperkalemia |

| Drug class and representative agents | Dosage | Recommendations | Side effects |
|---|---|---|---|
| **NSAIDs** | | | |
| Naproxen sodium (Anaprox) | 275 to 550 mg twice daily | Effective in alleviating various physical symptoms of PMS. Any NSAID should be effective. | Nausea, gastric ulceration, renal dysfunction. Use with caution in women with preexisting gastrointestinal or renal disease. |
| Mefenamic acid (Ponstel) | 250 mg tid with meals | | |
| **Androgens** | | | |
| Danazol (Danocrine) | 100 to 400 mg twice daily | Somewhat effective in alleviating mastalgia when taken during luteal phase. | Weight gain, decreased breast size, deepening of voice. Monitor lipid profile and liver function. |
| **GnRH agonists** | | | |
| Leuprolide (Lupron) | 3.75 mg IM every month or 11.25 mg IM every three months | Somewhat effective in alleviating physical and behavioral symptoms of PMS Side effect profile and cost limit use. | Hot flashes, cardiovascular effects, and osteoporosis |
| Goserelin (Zoladex) | 3.6 mg SC every month or 10.8 mg SC every three months | | |
| Nafarelin (Synarel) | 200 to 400 mcg intranasally twice daily | | |

**D.Diuretics.** Spironolactone (Aldactone) is the only diuretic that has been shown to effectively relieve breast tenderness and fluid retention. Spironolactone is administered only during the luteal phase.

**E.Prostaglandin Inhibitors.** Nonsteroidal anti-inflammatory drugs (NSAIDs) are traditional therapy for primary dysmenorrhea and menorrhagia. These agents include mefenamic acid (Ponstel) and naproxen sodium (Anaprox, Aleve).

**References:** See page 255.

## Primary Amenorrhea

Amenorrhea (absence of menses) results from dysfunction of the hypothalamus, pituitary, ovaries, uterus, or vagina. It is often classified as either primary (absence of menarche by age 16) or secondary (absence of menses for more than three cycle intervals or six months in women who were previously menstruating).

**I.Etiology**

**A.**Primary amenorrhea is usually the result of a genetic or anatomic abnormality. Common etiologies of primary amenorrhea:

**1.**Chromosomal abnormalities causing gonadal dysgenesis: 45 percent
**2.**Physiologic delay of puberty: 20 percent
**3.**Müllerian agenesis: 15 percent
**4.**Transverse vaginal septum or imperforate hymen: 5 percent
**5.**Absent production of gonadotropin-releasing hormone (GnRH) by the hypothalamus: 5 percent
**6.**Anorexia nervosa: 2 percent
**7.**Hypopituitarism: 2 percent

| Causes of Primary and Secondary Amenorrhea | |
|---|---|
| **Abnormality** | **Causes** |
| **Pregnancy** | |
| **Anatomic abnormalities** | |
| Congenital abnormality in Mullerian development | Isolated defect<br>Testicular feminization syndrome<br>5-Alpha-reductase deficiency<br>Vanishing testes syndrome<br>Defect in testis determining factor |
| Congenital defect of urogenital sinus development | Agenesis of lower vagina<br>Imperforate hymen |
| Acquired ablation or scarring of the endometrium | Asherman's syndrome<br>Tuberculosis |
| **Disorders of hypothalamic-pituitary ovarian axis**<br>Hypothalamic dysfunction<br>Pituitary dysfunction<br>Ovarian dysfunction | |

| Causes of Amenorrhea due to Abnormalities in the Hypothalamic-Pituitary-Ovarian Axis | |
|---|---|
| **Abnormality** | **Causes** |
| Hypothalamic dysfunction | Functional hypothalamic amenorrhea<br>Weight loss, eating disorders<br>Exercise<br>Stress<br>Severe or prolonged illness<br>Congenital gonadotropin-releasing hormone deficiency<br>Inflammatory or infiltrative diseases<br>Brain tumors - eg, craniopharyngioma<br>Pituitary stalk dissection or compression<br>Cranial irradiation<br>Brain injury - trauma, hemorrhage, hydrocephalus<br>Other syndromes - Prader-Willi, Laurence-Moon-Biedl |
| Pituitary dysfunction | Hyperprolactinemia<br>Other pituitary tumors- acromegaly, corticotroph adenomas (Cushing's disease)<br>Other tumors - meningioma, germinoma, glioma<br>Empty sella syndrome<br>Pituitary infarct or apoplexy |
| Ovarian dysfunction | Ovarian failure (menopause)<br>Spontaneous<br>Premature (before age 40 years)<br>Surgical |
| Other | Hyperthyroidism<br>Hypothyroidism<br>Diabetes mellitus<br>Exogenous androgen use |

**II. Diagnostic evaluation of primary amenorrhea**

**A. Step I: Evaluate clinical history**:

**1.** Signs of puberty may include a growth spurt, absence of axillary and pubic hair, or apocrine sweat glands, or absence of breast development. Lack of pubertal development suggests ovarian or pituitary failure or a chromosomal abnormality.

**2.** Family history of delayed or absent puberty suggests a familial disorder.

**3.** Short stature may indicate Turner syndrome or hypothalamic-pituitary disease.

**4.** Poor health may be a manifestation of hypothalamic-pituitary disease. Symptoms of other hypothalamic-pituitary disease include headaches, visual field defects, fatigue, or polyuria and polydipsia.

**5.** Virilization suggests polycystic ovary syndrome, an androgen-secreting ovarian or adrenal tumor, or the presence of Y chromosome material.

**6.** Recent stress, change in weight, diet, or exercise habits; or illness may suggest hypothalamic amenorrhea.

**7.** Heroin and methadone can alter hypothalamic gonadotropin secretion.

**8.** Galactorrhea is suggestive of excess prolactin. Some drugs cause amenorrhea by increasing serum prolactin concentrations, including metoclopramide and antipsychotic drugs.

**B. Step II: Physical examination**

**1.** An evaluation of pubertal development should include current height, weight, and arm span (normal arm span for adults is within 5 cm of height) and an evaluation of the growth chart.

**2.** Breast development should be assessed by Tanner staging.

**3.**The genital examination should evaluate clitoral size, pubertal hair development, intactness of the hymen, depth of the vagina, and presence of a cervix, uterus, and ovaries. If the vagina can not be penetrated with a finger, rectal examination may allow evaluation of the internal organs. Pelvic ultrasound is also useful to determine the presence or absence of müllerian structures.

**4.**The skin should be examined for hirsutism, acne, striae, increased pigmentation, and vitiligo.

**5.**Classic physical features of Turner syndrome include low hair line, web neck, shield chest, and widely spaced nipples.

**C.Step III: Basic laboratory testing**

**1.If a normal vagina or uterus are not obviously present** on physical examination, pelvic ultrasonography should be performed to confirm the presence or absence of ovaries, uterus, and cervix. Ultrasonography can be useful to exclude vaginal or cervical outlet obstruction in patients with cyclic pain.

**a.Uterus absent**

If the uterus is absent, evaluation should include a karyotype and serum testosterone. These tests should distinguish abnormal müllerian development (46, XX karyotype with normal female serum testosterone concentrations) from androgen insensitivity syndrome (46, XY karyotype and normal male serum testosterone concentrations).

Patients with 5-alpha reductase deficiency also have a 46, XY karyotype and normal male serum testosterone concentrations but, in contrast to the androgen insensitivity syndrome which is associated with a female phenotype, these patients undergo striking virilization at the time of puberty (secondary sexual hair, muscle mass, and deepening of the voice).

**1.Uterus present**. For patients with a normal vagina and uterus and no evidence of an imperforate hymen, vaginal septum, or congenital absence of the vagina. Measurement of serum beta human chorionic gonadotropin to exclude pregnancy and of serum FSH, prolactin, and TSH.

**a.**A high serum FSH concentration is indicative of primary ovarian failure. A karyotype is then required and may demonstrate complete or partial deletion of the X chromosome (Turner syndrome) or the presence of Y chromatin. The presence of a Y chromosome is associated with a higher risk of gonadal tumors and makes gonadectomy mandatory.

**b.**A low or normal serum FSH concentration suggests functional hypothalamic amenorrhea, congenital GnRH deficiency, or other disorders of the hypothalamic-pituitary axis. Cranial MR imaging is indicated in most cases of hypogonadotropic hypogonadism to evaluate hypothalamic or pituitary disease. Cranial MRI is recommended for all women with primary hypogonadotropic hypogonadism, visual field defects, or headaches.

**c.**Serum prolactin and thyrotropin (TSH) should be measured, especially if galactorrhea is present.

**d.**If there are signs or symptoms of hirsutism, serum testosterone and dehydroepiandrosterone sulfate (DHEA-S) should be measured to assess for an androgen-secreting tumor.

**e.**If hypertension is present, blood tests should be drawn for evaluate for CYP17 deficiency. The characteristic findings are elevations in serum progesterone (>3 ng/mL) and deoxycorticosterone and low values for serum 17-alpha-hydroxyprogesterone (<0.2 ng/mL).

**III.Treatment**

**A.**Treatment of primary amenorrhea is directed at correcting the underlying pathology; helping the woman to achieve fertility, if desired; and prevention of complications of the disease.

**B.Congenital anatomic lesions or Y chromosome material** usually requires surgery. Surgical correction of a vaginal outlet obstruction is necessary before menarche, or as soon as the diagnosis is made after menarche. Creation of a neovagina for patients with müllerian failure is usually delayed until the women is emotionally mature. If Y chromosome material is found, gonadectomy should be performed to prevent gonadal neoplasia. However, gonadectomy should be delayed until after puberty in patients with androgen insensitivity syndrome. These patients have a normal pubertal growth spurt and feminize at the time of expected puberty.

**C.Ovarian failure** requires counseling about the benefits and risks of hormone replacement therapy.

**D.Polycystic ovary syndrome** is managed with measures to reduce hirsutism, resume menses, and fertility and prevent of endometrial hyperplasia, obesity, and metabolic defects.

**E.Functional hypothalamic amenorrhea** can usually be reversed by weight gain, reduction in the intensity of exercise, or resolution of illness or emotional stress. For women who want to continue to exercise, estrogen-progestin replacement therapy should be given to those not seeking fertility to prevent osteoporosis. Women who want to become pregnant can be treated with gonadotropins or pulsatile GnRH.

**F.Hypothalamic or pituitary dysfunction** that is not reversible (eg, congenital GnRH deficiency) is treated with either exogenous gonadotropins or pulsatile GnRH if the woman wants to become pregnant.

**References:** See page 255.

# Breast Disorders

Breast pain, nipple discharge and a palpable mass are the most common breast problems for which women consult a physician.

**I.Nipple Discharge**

**A.Clinical evaluation**

**1.**Nipple discharge may be a sign of cancer; therefore, it must be thoroughly evaluated. About 8% of biopsies performed for nipple discharge demonstrate cancer. The duration, bilaterality or unilaterality of the discharge, and the presence of blood should be determined. A history of oral contraceptives, hormone preparations, phenothiazines, nipple or breast stimulation or lactation should be sought. Discharges that flow spontaneously are more likely to be pathologic than discharges that must be manually expressed.

**2.**Unilateral, pink colored, bloody or non-milky discharge, or discharges associated with a mass are the discharges of most concern. Milky discharge can be caused by oral contraceptive agents, estrogen replacement therapy, phenothiazines, prolactinoma, or hypothyroidism. Nipple discharge secondary to malignancy is more likely to occur in older patients.

**3.Risk factors.** The assessment should identify risk factors, including age over 50 years, past personal history of breast cancer, history of hyperplasia on previous breast biopsies, and family history of breast cancer in a first-degree relative (mother, sister, daughter).

**B.Physical examination** should include inspection of the breast for ulceration or contour changes and inspection of the nipple. Palpation should be performed with the patient in both the upright and the supine positions to determine the presence of a mass.

**C.Diagnostic evaluation**

**1.Bloody discharge.** A mammogram of the involved breast should be obtained if the patient is over 35 years old and has not had a mammogram within the preceding 6 months. Biopsy of any suspicious lesions should be completed.

**2.Watery, unilateral discharge** should be referred to a surgeon for evaluation and possible biopsy.

**3.Non-bloody discharge** should be tested for the presence of blood with a Hemoccult card. Nipple discharge secondary to carcinoma usually contains hemoglobin.

**4.Milky, bilateral discharge** should be evaluated with assays of prolactin and thyroid stimulating hormone to exclude an endocrinologic cause.

**a.**A mammogram should be performed if the patient is due for routine mammographic screening.

**b.**If results of the mammogram and the endocrinologic screening studies are normal, the patient should return for a follow-up visit in 6 months to ensure that there has been no specific change in the character of the discharge, such as development of bleeding.

**II.Breast Pain**

**A.**Breast pain is the most common breast symptom causing women to consult primary care physicians. Mastalgia is more common in premenopausal women than in postmenopausal women, and it is rarely a presenting symptom of breast cancer.

**B.**The evaluation of breast pain should determine the type of pain, its location and its relationship to the menstrual cycle. Most commonly, breast pain is associated with the menstrual cycle (cyclic mastalgia).

**C.**Cyclic pain is usually bilateral and poorly localized. The pain is often relieved after the menses. Cyclic breast pain occurs more often in younger women and resolves spontaneously.

**D.**Noncyclic mastalgia is most common in women 40 to 50 years of age. It is often a unilateral pain. Noncyclic mastalgia is occasionally secondary to the presence of a fibroadenoma or cyst, and the pain may be relieved by treatment of the underlying breast lesion.

**E.Evaluation.** A thorough breast examination should be performed to exclude the presence of a breast mass. Women 35 years of age and older should undergo mammography unless a mammogram was obtained in the past 12 months. If a suspicious lesion is detected, biopsy is required. When the physical examination is normal, imaging studies are not indicated in women younger than 35 years of age. A follow-up clinical breast examination should be performed in 1-2 months.

**F.Mastodynia**

**1.**Mastodynia is defined as breast pain in the absence of a mass or other pathologic abnormality.

**2.Causes of mastodynia** include menstrually related pain, costochondritis, trauma, and sclerosing adenosis.

**III.Fibrocystic Complex**

**A.**Breast changes are usually multifocal, bilateral, and diffuse. One or more isolated fibrocystic lumps or areas of asymmetry may be present. The areas are usually tender.

**B.**This disorder predominantly occurs in women with premenstrual abnormalities, nulliparous women, and nonusers of oral contraceptives.

**C.**The disorder usually begins in mid-20's or early 30's. Tenderness is associated with menses and lasts about a week. The upper outer quadrant of the breast is most frequently involved bilaterally. There is no increased risk of cancer for the majority of patients.

**D.**Suspicious areas may be evaluated by fine needle aspiration (FNA) cytology. If mammography and FNA are negative for cancer, and the clinical examination is benign, open biopsy is generally not needed.

**E.Medical management of fibrocystic complex**

**1.Oral contraceptives** are effective for severe breast pain in most young women. Start with a pill that contains low amounts of estrogen and relatively high amounts of progesterone (Loestrin, LoOvral, Ortho-Cept).

**2.**If oral contraceptives do not provide relief, medroxyprogesterone, 5-10 mg/day from days 15-25 of each cycle, is added.

**3.**A professionally fitted support bra often provides significant relief.

**4.Danazol (Danocrine),** an antigonadotropin, has a response rate of 50 to 75 percent in women with cyclic pain who received danazol in a dosage of 100 to 400 mg per day. Danazol therapy is recommended only for patients with severe, activity-limiting pain. Side effects include menstrual irregularity, acne, weight gain and hirsutism.

**5.Evening primrose oil** (g-linolenic acid) is effective in about 38 to 58 percent of patients with mastalgia; 2 - 4 g per day.

**IV.Breast Masses**

**A.**The normal glandular tissue of the breast is nodular. Nodularity is a physiologic process and is not an indication of breast pathology. Dominant masses may be discrete or poorly defined, but they differ in character from the surrounding breast tissue. The differential diagnosis of a dominant breast mass includes macrocyst (clinically evident cyst), fibroadenoma, prominent areas of fibrocystic change, fat necrosis and cancer.

**B.Cystic Breast Masses**

**1.**Cysts are a common cause of dominant breast masses in premenopausal women more than 40 years of age, but they are an infrequent cause of such masses in younger women. Cysts are usually well demarcated, firm and mobile.

**2.**Ultrasonography or aspiration must establish a definitive diagnosis for a cyst. Cysts require surgical biopsy if the aspirated fluid is bloody, the palpable abnormality does not resolve completely after the aspiration of fluid or the same cyst recurs multiple times in a short period of time. Routine cytologic examination of cyst fluid is not indicated.

**3.Nonpalpable cysts** identified by mammography and confirmed to be simple cysts by ultrasound examination require no treatment.

**C.Solid Breast Masses**

**1.**Noncystic masses in premenopausal women that are clearly different from the surrounding breast tissue require histologic sampling by fine-needle aspiration, core cutting, needle biopsy or excisional biopsy.

**2.Solid Masses in Women Less Than 40 Years of Age**

**a.**If the physical examination reveals no evidence of a dominant breast mass, the patient should be reassured and instructed in breast self-examination. If the clinical significance of a physical finding is uncertain, a directed ultrasound examination is performed. If this examination does not demonstrate a mass, the physical examination is repeated in two to four months. In women 35 to 40 years of age who have a normal ultrasound examination, a mammogram may also be obtained.

**b.**A suspicious mass is solitary, discrete, hard and adherent to adjacent tissue. Mammography should be performed before obtaining a pathologic diagnosis.

**c.**If a clinically benign mass is present, an ultrasound examination and fine-needle aspiration are performed to confirm that the mass is benign. This approach is the "triple test" (clinical examination, ultrasonography [or mammography] and fine-needle aspiration).

**3.Solid Masses in Women More Than 40 Years of Age.** Abnormalities detected on physical examination in older women should be regarded as possible cancers until they are proven to be benign. In women more than 40 years of age, diagnostic mammography is a standard part of the evaluation of a solid breast mass.

**References:** See page 255.

# Menopause

Menopause is defined as the cessation of menstrual periods in women. The average age of menopause is 51 years, with a range of 41-55. The diagnosis of menopause is made by the presence of amenorrhea for six to twelve months, together with the occurrence of hot flashes. If the diagnosis is in doubt, menopause is indicated by an elevated follicle-stimulating hormone (FSH) level greater than 40 mIU/mL.

**I.Perimenopausal transition** is defined as the two to eight years preceding menopause and the one year after the last menstrual period. It is characterized by normal ovulatory cycles interspersed with anovulatory (estrogen-only) cycles. As a result, menses become irregular, and heavy breakthrough bleeding, termed dysfunctional uterine bleeding, can occur during longer periods of anovulation.

**II.Effects of estrogen deficiency after menopause**

**A.Hot flashes.** The most common acute change during menopause is the hot flash, which occurs in 75 percent of women. About 50 to 75 percent of women have cessation of hot flashes within five years. Hot flashes typically begin as a sudden sensation of heat centered on the face and upper chest that rapidly becomes generalized. The sensation lasts from two to four minutes and is often associated with profuse perspiration. Hot flashes occur several times per day.

**B.Sexual function**. Estrogen deficiency leads to a decrease in blood flow to the vagina and vulva. This decrease is a major cause of decreased vaginal lubrication, dyspareunia, and decreased sexual function in menopausal women.

**C.Urinary incontinence.** Menopause results in atrophy of the urethral epithelium with subsequent atrophic urethritis and irritation; these changes predispose to both stress and urge urinary incontinence.

**D.Osteoporosis.** A long-term consequence of estrogen deficiency is the development of osteoporosis and frac-

tures. Bone loss exceeds bone reformation. Between 1 and 5 percent of the skeletal mass can be lost per year in the first several years after the menopause. Osteoporosis may occur in as little as ten years.

**E.Cardiovascular disease.** The incidence of myocardial infarction in women, although lower than in men, increases dramatically after the menopause.

**III.Estrogen replacement therapy**

**A.**Data from the WHI and the HERS trials has determined that continuous estrogen-progestin therapy does not appear to protect against cardiovascular disease and increases the risk of breast cancer, coronary heart disease, stroke, and venous thromboembolism over an average follow-up of 5.2 years. As a result, the primary indication for estrogen therapy is for control of menopausal symptoms, such as hot flashes.

**IV.Prevention and treatment of osteoporosis**

**A.Screening for osteoporosis**. Measurement of BMD is recommended for all women 65 years and older regardless of risk factors. BMD should also be measured in all women under the age of 65 years who have one or more risk factors for osteoporosis (in addition to menopause). The hip is the recommended site of measurement.

**B.Bisphosphonates**

**1.Alendronate (Fosamax)** has effects comparable to those of estrogen for both the treatment of osteoporosis (10 mg/day or 70 mg once a week) and for its prevention (5 mg/day). Alendronate (in a dose of 5 mg/day or 35 mg/week) can also prevent osteoporosis in postmenopausal women.

**2.Risedronate (Actonel)**, a bisphosphonate, has been approved for prevention and treatment of osteoporosis at doses of 5 mg/day or 35 mg once per week. Its efficacy and side effect profile are similar to those of alendronate.

**C.Raloxifene (Evista)** is a selective estrogen receptor modulator. It is available for prevention and treatment of osteoporosis. At a dose of 60 mg/day, bone density increases by 2.4 percent in the lumbar spine and hip over a two year period. This effect is slightly less than with bisphosphonates.

**D.Calcium.** Maintaining a positive calcium balance in postmenopausal women requires a daily intake of 1500 mg of elemental calcium; to meet this most women require a supplement of 1000 mg daily.

**E.Vitamin D.** All postmenopausal women should take a multivitamin containing at least 400 IU vitamin D daily.

**F.Exercise** for at least 20 minutes daily reduces the rate of bone loss. Weight bearing exercises are preferable.

**V.Treatment of hot flashes and vasomotor instability**

**A.**The manifestations of vasomotor instability are hot flashes, sleep disturbances, headache, and irritability. Most women with severe vasomotor instability accept short-term estrogen therapy for these symptoms.

**B.Short-term estrogen therapy for relief of vasomotor instability and hot flashes**

**1.**Short-term estrogen therapy remains the best treatment for relief of menopausal symptoms, and therefore is recommended for most postmenopausal women, with the exception of those with a history of breast cancer, CHD, a previous venous thromboembolic event or stroke, or those at high risk for these complications. Short-term therapy is continued for six months to four or five years. Administration of estrogen short-term is not associated with an increased risk of breast cancer.

**2.**Low dose estrogen is recommended (eg, 0.3 mg conjugated estrogens [Premarin] daily or 0.5 mg estradiol [Estrace] daily). These doses are adequate for symptom management and prevention of bone loss.

**3.**Endometrial hyperplasia and cancer can occur after as little as six months of unopposed estrogen therapy; as a result, a progestin must be added in those women who have not had a hysterectomy. Medroxyprogesterone (Provera), 2.5 mg, is usually given every day of the month.

**4.**After the planned treatment interval, the estrogen should be discontinued gradually to minimize recurrence of the menopausal symptoms, for example, by omitting one pill per week (6 pills per week, 5 pills per week, 4 pills per week).

**C.Treatment of vasomotor instability in women not taking estrogen**

**1.Selective serotonin reuptake inhibitors** (SSRIs) also relieve the symptoms of vasomotor instability.

**a.Venlafaxine (Effexor)**, at doses of 75 mg daily, reduces hot flashes by 61 percent. Mouth dryness, anorexia, nausea, and constipation are common.

**b.Paroxetine (Zoloft)**, 50 mg per day, relieves vasomotor instability.

**c.Fluoxetine (Prozac)** 20 mg per day also has beneficial effects of a lesser magnitude.

**2.Clonidine (Catapres)** relieves hot flashes in 80%. In a woman with hypertension, clonidine might be considered as initial therapy. It is usually given as a patch containing 2.5 mg per week. Clonidine also may be given orally in doses of 0.1 to 0.4 mg daily. Side effects often limit the use and include dry mouth, dizziness, constipation, and sedation.

**3.Megestrol acetate (Megace)** is a synthetic progestin which decreases the frequency of hot flashes by 85 percent at a dose of 40 to 80 mg PO daily. Weight gain is the major side effect.

**VI.Treatment of urogenital atrophy**

**A.**Loss of estrogen causes atrophy of the vaginal epithelium and results in vaginal irritation and dryness, dyspareunia, and an increase in vaginal infections. Systemic estrogen therapy results in relief of symptoms.

**B.Treatment of urogenital atrophy in women not taking systemic estrogen**

**1.Moisturizers and lubricants**. Regular use of a vaginal moisturizing agent (Replens) and lubricants during intercourse are helpful. Water soluble lubricants such as

Astroglide are more effective than lubricants that become more viscous after application such as K-Y jelly. A more effective treatment is vaginal estrogen therapy.

**2.Low-dose vaginal estrogen**

**a.Vaginal ring estradiol (Estring)**, a silastic ring impregnated with estradiol, is the preferred means of delivering estrogen to the vagina. The silastic ring delivers 6 to 9 µg of estradiol to the vagina daily for a period of three months. The rings are changed once every three months by the patient. Concomitant progestin therapy is not necessary.

**b.Conjugated estrogens (Premarin)**, 0.5 gm of cream, or one-eighth of an applicatorful daily into the vagina for three weeks, followed by twice weekly thereafter. Concomitant progestin therapy is not necessary.

**c.Estrace cream (estradiol)** can also by given by vaginal applicator at a dose of one-eighth of an applicator or 0.5 g (which contains 50 µg of estradiol) daily into the vagina for three weeks, followed by twice weekly thereafter. Concomitant progestin therapy is not necessary.

**d.Estradiol (Vagifem).** A tablet containing 25 micrograms of estradiol is available and is inserted into the vagina twice per week. Concomitant progestin therapy is not necessary.

**References:** See page 255.

# Osteoporosis

Over 1.3 million osteoporotic fractures occur each year in the United States. The risk of all fractures increases with age; among persons who survive until age 90, 33 percent of women will have a hip fracture. The lifetime risk of hip fracture for white women at age 50 is 16 percent. Osteoporosis is characterized by low bone mass, microarchitectural disruption, and increased skeletal fragility.

**Risk Factors for Osteoporotic Fractures**

| | |
|---|---|
| Personal history of fracture as an adult | White race |
| History of fracture in a first-degree relative | Advanced age |
| Current cigarette smoking | Lifelong low calcium intake |
| Low body weight (less than 58 kg [127 lb]) | Alcoholism |
| Female sex | Inadequate physical activity |
| Estrogen deficiency (menopause before age 45 years or bilateral ovariectomy, prolonged premenopausal amenorrhea [greater than one year]) | Recurrent falls |
| | Dementia |
| | Impaired eyesight despite adequate correction |
| | Poor health/frailty |

**I.Screening for osteoporosis and osteopenia**

**A.Normal bone density** is defined as a bone mineral density (BMD) value within one standard deviation of the mean value in young adults of the same sex and race.

**B.Osteopenia** is defined as a BMD between 1 and 2.5 standard deviations below the mean.

**C.Osteoporosis** is defined as a value more than 2.5 standard deviations below the mean; this level is the fracture threshold. These values are referred to as T-scores (number of standard deviations above or below the mean value).

**D.Dual x-ray absorptiometry**. In dual x-ray absorptiometry (DXA), two photons are emitted from an x-ray tube. DXA is the most commonly used method for measuring bone density because it gives very precise measurements with minimal radiation. DXA measurements of the spine and hip are recommended.

**E.Biochemical markers of bone turnover**. **Urinary deoxypyridinoline (DPD) and urinary alpha-1 to alpha-2 N-telopeptide of collagen (NTX)** are the most specific and clinically useful markers of bone resorption. Biochemical markers are not useful for the screening or diagnosis of osteoporosis because the values in normal and osteoporosis overlap substantially.

**II.Recommendations for screening for osteoporosis of the National Osteoporosis Foundation**

**A.**All women should be counseled about the risk factors for osteoporosis, especially smoking cessation and limiting alcohol. All women should be encouraged to participate in regular weight-bearing and exercise.

**B.**Measurement of BMD is recommended for all women 65 years and older regardless of risk factors. BMD should also be measured in all women under the age of 65 years who have one or more risk factors for osteoporosis (in addition to menopause). The hip is the recommended site of measurement.

**C.**All adults should be advised to consume at least 1,200 mg of calcium per day and 400 to 800 IU of vitamin D per day. A daily multivitamin (which provides 400 IU) is recommended. In patients with documented vitamin D deficiency, osteoporosis, or previous fracture, two multivitamins may be reasonable, particularly if dietary intake is inadequate and access to sunlight is poor.

**D.**Treatment is recommended for women without risk factors who have a BMD that is 2 SD below the mean for young women, and in women with risk factors who have a BMD that is 1.5 SD below the mean.

**III.Nonpharmacologic therapy of osteoporosis in women**

**A.Diet.** An optimal diet for treatment (or prevention) of osteoporosis includes an adequate intake of calories (to avoid malnutrition), calcium, and vitamin D.

**B.Calcium.** Postmenopausal women should be advised to take 1000 to 1500 mg/day of elemental calcium, in divided doses, with meals.

**C.Vitamin D** total of 800 IU daily should be taken.

**D.Exercise**. Women should exercise for at least 30 minutes three times per week. Any weight-bearing exercise regimen, including walking, is acceptable.

**E.Cessation of smoking** is recommended for all women because smoking cigarettes accelerates bone loss.

**IV.Drug therapy of osteoporosis in women**

**A.**Selected postmenopausal women with osteoporosis or at high risk for the disease should be considered for drug therapy. Particular attention should be paid to treating women with a recent fragility fracture, including hip fracture, because they are at high risk for a second fracture.

**B.**Candidates for drug therapy are women who already have postmenopausal osteoporosis (less than -2.5) and women with osteopenia (T score -1 to -2.5) soon after menopause.

**C.Bisphosphonates**

**1.Alendronate (Fosamax)** (10 mg/day or 70 mg once weekly) or **risedronate (Actonel)** (5 mg/day or 35 mg once weekly) are good choices for the treatment of osteoporosis. Bisphosphonate therapy increases bone mass and reduces the incidence of vertebral and nonvertebral fractures.

**2.**Alendronate (5 mg/day or 35 mg once weekly) and risedronate (5 mg/day of 35 mg once weekly) have been approved for prevention of osteoporosis.

**3.**Alendronate or risedronate should be taken with a full glass of water 30 minutes before the first meal or beverage of the day. Patients should not lie down for at least 30 minutes after taking the dose to avoid the unusual complication of pill-induced esophagitis.

**4.**Alendronate is well tolerated and effective for at least seven years.

**5.**The bisphosphonates (alendronate or risedronate) and raloxifene are first-line treatments for *prevention* of osteoporosis. The bisphosphonates are first-line therapy for *treatment* of osteoporosis. Bisphosphonates are preferred for prevention and treatment of osteoporosis because they increase bone mineral density more than raloxifene.

**D.Selective estrogen receptor modulators**

**1.Raloxifene (Evista)** (5 mg daily or a once-a-week preparation) is a selective estrogen receptor modulator (SERM) for prevention and treatment of osteoporosis. It increases bone mineral density and reduces serum total and low-density-lipoprotein (LDL) cholesterol. It also appears to reduce the incidence of vertebral fractures and is one of the first-line drugs for prevention of osteoporosis.

**2.**Raloxifene is somewhat less effective than the bisphosphonates for the prevention and treatment of osteoporosis. Venous thromboembolism is a risk.

**Treatment Guidelines for Osteoporosis**

Calcium supplements with or without vitamin D supplements or calcium-rich diet
Weight-bearing exercise
Avoidance of alcohol tobacco products
Alendronate (Fosamax)
Risedronate (Actonel)
Raloxifene (Evista)

**Agents for Treating Osteoporosis**

| Medication | Dosage | Route |
|---|---|---|
| Calcium | 1,000 to 1,500 mg per day | Oral |
| Vitamin D | 400 IU per day (800 IU per day in winter in northern latitudes) | Oral |
| Alendronate (Fosamax) | **Prevention:** 5 mg per day or 35 mg once-a-week<br>**Treatment:** 10 mg per day or 70 mg once-a-week | Oral |
| Risedronate (Actonel) | 5 mg daily or 35 mg once weekly | Oral |
| Raloxifene (Evista) | 60 mg per day | Oral |
| Conjugated estrogens | 0.3 mg per day | Oral |

**E.Monitoring the response to therapy**

**1.**Bone mineral density and a marker of bone turnover should be measured at baseline, followed by a repeat measurement of the marker in three months.

**2.**If the marker falls appropriately, the drug is having the desired effect, and therapy should be continued for two years, at which time bone mineral density can be measured again. The anticipated three-month decline in markers is 50 percent with alendronate.

**F.Estrogen/progestin therapy**

**1.**Estrogen-progestin therapy is no longer a first-line approach for the treatment of osteoporosis in postmenopausal women because of increases in the risk of breast cancer, stroke, venous thromboembolism, and coronary disease.

**2.**Indications for estrogen-progestin in postmenopausal women include persistent menopausal symptoms and patients with an indication for antiresorptive therapy who cannot tolerate the other drugs.

**References:** See page 255.

# Abnormal Vaginal Bleeding

Menorrhagia (excessive bleeding) is most commonly caused by anovulatory menstrual cycles. Occasionally it is caused by thyroid dysfunction, infections or cancer.

**I. Pathophysiology of normal menstruation**

**A.** In response to gonadotropin-releasing hormone from the hypothalamus, the pituitary gland synthesizes follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which induce the ovaries to produce estrogen and progesterone.

**B.** During the follicular phase, estrogen stimulation causes an increase in endometrial thickness. After ovulation, progesterone causes endometrial maturation. Menstruation is caused by estrogen and progesterone withdrawal.

**C. Abnormal bleeding** is defined as bleeding that occurs at intervals of less than 21 days, more than 36 days, lasting longer than 7 days, or blood loss greater than 80 mL.

**II. Clinical evaluation of abnormal vaginal bleeding**

**A.** A menstrual and reproductive history should include last menstrual period, regularity, duration, frequency; the number of pads used per day, and intermenstrual bleeding.

**B.** Stress, exercise, weight changes and systemic diseases, particularly thyroid, renal or hepatic diseases or coagulopathies, should be sought. The method of birth control should be determined.

**C.** Pregnancy complications, such as spontaneous abortion, ectopic pregnancy, placenta previa and abruptio placentae, can cause heavy bleeding. Pregnancy should always be considered as a possible cause of abnormal vaginal bleeding.

**III. Puberty and adolescence--menarche to age 16**

**A.** Irregularity is normal during the first few months of menstruation; however, soaking more than 25 pads or 30 tampons during a menstrual period is abnormal.

**B.** Absence of premenstrual symptoms (breast tenderness, bloating, cramping) is associated with anovulatory cycles.

**C.** Fever, particularly in association with pelvic or abdominal pain may, indicate pelvic inflammatory disease. A history of easy bruising suggests a coagulation defect. Headaches and visual changes suggest a pituitary tumor.

**D. Physical findings**

**1.** Pallor not associated with tachycardia or signs of hypovolemia suggests chronic excessive blood loss secondary to anovulatory bleeding, adenomyosis, uterine myomas, or blood dyscrasia.

**2.** Fever, leukocytosis, and pelvic tenderness suggests PID.

**3.** Signs of impending shock indicate that the blood loss is related to pregnancy (including ectopic), trauma, sepsis, or neoplasia.

**4.** Pelvic masses may represent pregnancy, uterine or ovarian neoplasia, or a pelvic abscess or hematoma.

**5.** Fine, thinning hair, and hypoactive reflexes suggest hypothyroidism.

**6.** Ecchymoses or multiple bruises may indicate trauma, coagulation defects, medication use, or dietary extremes.

**E. Laboratory tests**

**1.** CBC and platelet count and a urine or serum pregnancy test should be obtained.

**2.** Screening for sexually transmitted diseases, thyroid function, and coagulation disorders (partial thromboplastin time, INR, bleeding time) should be completed.

**3. Endometrial sampling** is rarely necessary for those under age 20.

**F. Treatment of infrequent bleeding**

**1.** Therapy should be directed at the underlying cause when possible. If the CBC and other initial laboratory tests are normal and the history and physical examination are normal, reassurance is usually all that is necessary.

**2.** Ferrous gluconate, 325 mg bid-tid, should be prescribed.

**G. Treatment of frequent or heavy bleeding**

**1.** Treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) improves platelet aggregation and increases uterine vasoconstriction. NSAIDs are the first choice in the treatment of menorrhagia because they are well tolerated and do not have the hormonal effects of oral contraceptives.

**a. Mefenamic acid (Ponstel)** 500 mg tid during the menstrual period.

**b. Naproxen (Anaprox, Naprosyn)** 500 mg loading dose, then 250 mg tid during the menstrual period.

**c. Ibuprofen (Motrin, Nuprin)** 400 mg tid during the menstrual period.

**d.** Gastrointestinal distress is common. NSAIDs are contraindicated in renal failure and peptic ulcer disease.

**2.** Iron should also be added as ferrous gluconate 325 mg tid.

**H. Patients with hypovolemia or a hemoglobin level below 7 g/dL** should be hospitalized for hormonal therapy and iron replacement.

**1.** Hormonal therapy consists of estrogen (Premarin) 25 mg IV q6h until bleeding stops. Thereafter, oral contraceptive pills should be administered q6h x 7 days, then taper slowly to one pill qd.

**2.** If bleeding continues, IV vasopressin (DDAVP) should be administered. Hysteroscopy may be necessary, and dilation and curettage is a last resort. Transfusion may be indicated in severe hemorrhage.

**3.** Iron should also be added as ferrous gluconate 325 mg tid.

**IV. Primary childbearing years – ages 16 to early 40s**

**A.** Contraceptive complications and pregnancy are the most common causes of abnormal bleeding in this age group. Anovulation accounts for 20% of cases.

**B.** Adenomyosis, endometriosis, and fibroids increase in frequency as a woman ages, as do endometrial hyperplasia and endometrial polyps. Pelvic inflammatory disease and endocrine dysfunction may also occur.

**C. Laboratory tests**

**1.** CBC and platelet count, Pap smear, and pregnancy test.

**2.** Screening for sexually transmitted diseases, thyroid-stimulating hormone, and coagulation disorders (partial thromboplastin time, INR, bleeding time).

**3.** If a non-pregnant woman has a pelvic mass, ultrasonography or hysterosonography (with uterine saline infusion) is required.

**D. Endometrial sampling**

**1.** Long-term unopposed estrogen stimulation in anovulatory patients can result in endometrial hyperplasia, which can progress to adenocarcinoma; therefore, in perimenopausal patients who have been anovulatory for an extended interval, the endometrium should be biopsied.

**2.** Biopsy is also recommended before initiation of hormonal therapy for women over age 30 and for those over age 20 who have had prolonged bleeding.

**3.** Hysteroscopy and endometrial biopsy with a Pipelle aspirator should be done on the first day of menstruation (to avoid an unexpected pregnancy) or anytime if bleeding is continuous.

**E. Treatment**

**1.** Medical protocols for anovulatory bleeding (dysfunctional uterine bleeding) are similar to those described above for adolescents.

**2. Hormonal therapy**

**a.** In women who do not desire immediate fertility, hormonal therapy may be used to treat menorrhagia.

**b.** A 21-day package of oral contraceptives is used. The patient should take one pill three times a day for 7 days. During the 7 days of therapy, bleeding should subside, and, following treatment, heavy flow will occur. After 7 days off the hormones, another 21-day package is initiated, taking one pill each day for 21 days, then no pills for 7 days.

**c.** Alternatively, medroxyprogesterone (Provera), 10-20 mg per day for days 16 through 25 of each month, will result in a reduction of menstrual blood loss. Pregnancy will not be prevented.

**d.** Patients with severe bleeding may have hypotension and tachycardia. These patients require hospitalization, and estrogen (Premarin) should be administered IV as 25 mg q4-6h until bleeding slows (up to a maximum of four doses). Oral contraceptives should be initiated concurrently as described above.

**3.** Iron should also be added as ferrous gluconate 325 mg tid.

**4.** Surgical treatment can be considered if childbearing is completed and medical management fails to provide relief.

**V. Premenopausal, perimenopausal, and postmenopausal years--age 40 and over**

**A.** Anovulatory bleeding accounts for about 90% of abnormal vaginal bleeding in this age group. However, bleeding should be considered to be from cancer until proven otherwise.

**B.** History, physical examination and laboratory testing are indicated as described above. Menopausal symptoms, personal or family history of malignancy and use of estrogen should be sought. A pelvic mass requires an evaluation with ultrasonography.

**C. Endometrial carcinoma**

**1.** In a perimenopausal or postmenopausal woman, amenorrhea preceding abnormal bleeding suggests endometrial cancer. Endometrial evaluation is necessary before treatment of abnormal vaginal bleeding.

**2.** Before endometrial sampling, determination of endometrial thickness by transvaginal ultrasonography is useful because biopsy is often not required when the endometrium is less than 5 mm thick.

**D. Treatment**

**1.** Cystic hyperplasia or endometrial hyperplasia without cytologic atypia is treated with depo-medroxyprogesterone, 200 mg IM, then 100 to 200 mg IM every 3 to 4 weeks for 6 to 12 months. Endometrial hyperplasia requires repeat endometrial biopsy every 3 to 6 months.

**2.** Atypical hyperplasia requires fractional dilation and curettage, followed by progestin therapy or hysterectomy.

**3.** If the patient's endometrium is normal (or atrophic) and contraception is a concern, a low-dose oral contraceptive may be used. If contraception is not needed, estrogen and progesterone therapy should be prescribed.

**4. Surgical management**

**a. Vaginal or abdominal hysterectomy** is the most absolute curative treatment.

**b. Dilatation and curettage** can be used as a temporizing measure to stop bleeding.

**c. Endometrial ablation and resection** by laser, electrodiathermy "rollerball," or excisional resection are alternatives to hysterectomy.

**References:** See page 255.

# Pelvic Inflammatory Disease

Pelvic inflammatory disease (PID) is an acute infection of the upper genital tract in women, involving any or all of the uterus, oviducts, and ovaries. PID is a community-acquired infection initiated by a sexually transmitted agent. Pelvic inflammatory disease accounts for approximately 2.5 million outpatient visits and 200,000 hospitalizations annually.

## I.Clinical evaluation

**A.**Lower abdominal pain is the cardinal presenting symptom in women with PID, although the character of the pain may be quite subtle. The onset of pain during or shortly after menses is particularly suggestive. The abdominal pain is usually bilateral and rarely of more than two weeks' duration.

**B.**Abnormal uterine bleeding occurs in one-third or more of patients with PID. New vaginal discharge, urethritis, proctitis, fever, and chills can be associated signs.

**C.Risk factors for PID:**

**1.**Age less than 35 years
**2.**Nonbarrier contraception
**3.**New, multiple, or symptomatic sexual partners
**4.**Previous episode of PID
**5.**Oral contraception
**6.**African-American ethnicity

## II.Physical examination

**A.**Only one-half of patients with PID have fever. Abdominal examination reveals diffuse tenderness greatest in the lower quadrants, which may or may not be symmetrical. Rebound tenderness and decreased bowel sounds are common. Tenderness in the right upper quadrant does not exclude PID, because approximately 10 percent of these patients have perihepatitis (Fitz-Hugh Curtis syndrome).

**B.**Purulent endocervical discharge and/or acute cervical motion and adnexal tenderness by bimanual examination is strongly suggestive of PID. Rectovaginal examination should reveal the uterine adnexal tenderness.

## III.Diagnosis

**A.Diagnostic criteria and guidelines**. The index of suspicion for the clinical diagnosis of PID should be high, especially in adolescent women.

**B.**The CDC has recommended minimum criteria required for empiric treatment of PID. These major determinants include lower abdominal tenderness, adnexal tenderness, and cervical motion tenderness. Minor determinants (ie, signs that may increase the suspicion of PID) include:

**1.**Fever (oral temperature >101°F; >38.3°C)
**2.**Vaginal discharge
**3.**Documented STD
**4.**Erythrocyte sedimentation rate (ESR)
**5.**C-reactive protein
**6.**Systemic signs
**7.**Dyspareunia

**C.Empiric treatment for pelvic inflammatory disease is recommended when:**

**1.**The examination suggests PID
**2.**Demographics (risk factors) are consistent with PID
**3.**Pregnancy test is negative

**Laboratory Evaluation for Pelvic Inflammatory Disease**

- Pregnancy test
- Microscopic exam of vaginal discharge in saline
- Complete blood counts
- Tests for chlamydia and gonococcus
- Urinalysis
- Fecal occult blood test
- C-reactive protein(optional)

## IV.Diagnostic testing

**A.Laboratory testing** for patients suspected of having PID always begins with a pregnancy test to rule out ectopic pregnancy and complications of an intrauterine pregnancy. A urinalysis and a stool for occult blood should be obtained because abnormalities in either reduce the probability of PID. Blood counts have limited value. Fewer than one-half of PID patients exhibit leukocytosis.

**B.**Gram stain and microscopic examination of vaginal discharge may provide useful information. If a cervical Gram stain is positive for Gram-negative intracellular diplococci, the probability of PID greatly increases; if negative, it is of little use.

**C.**Increased white blood cells (WBC) in vaginal fluid may be the most sensitive single laboratory test for PID (78 percent for $\geq$3 WBC per high power field. However, the specificity is only 39 percent.

**D.Recommended laboratory tests:**

**1.**Pregnancy test
**2.**Microscopic exam of vaginal discharge in saline
**3.**Complete blood counts
**4.**Tests for chlamydia and gonococcus
**5.**Urinalysis
**6.**Fecal occult blood test
**7.**C-reactive protein(optional)

**E.**Ultrasound imaging is reserved for acutely ill patients with PID in whom a pelvic abscess is a consideration.

## V.Recommendations

**A.**Health care providers should maintain a low threshold for the diagnosis of PID, and sexually active young women with lower abdominal, adnexal, and cervical motion tenderness should receive empiric treatment. The specificity of these clinical criteria can be enhanced by the presence of fever, abnormal cervical/vaginal discharge, elevated ESR and/or serum C-reactive protein, and the demonstration of cervical gonorrhea or chlamydia infection.

**B.**If clinical findings (epidemiologic, symptomatic, and physical examination) suggest PID empiric treatment should be initiated.

| Differential Diagnosis of Pelvic Inflammatory Disease | |
|---|---|
| Appendicitis<br>Ectopic pregnancy<br>Hemorrhagic ovarian cyst<br>Ovarian torsion<br>Endometriosis<br>Urinary tract Infection | Irritable bowel syndrome<br>Somatization<br>Gastroenteritis<br>Cholecystitis<br>Nephrolithiasis |

**VI. Treatment of pelvic inflammatory disease**

**A.** The two most important initiators of PID, Neisseria gonorrhoeae and Chlamydia trachomatis, must be treated, but coverage should also be provided for groups A and B streptococci, Gram negative enteric bacilli (Escherichia coli, Klebsiella spp., and Proteus spp.), and anaerobes.

**B. Outpatient therapy**

**1.** For outpatient therapy, the CDC recommends either oral ofloxacin (Floxin, 400 mg twice daily) or levofloxacin (Levaquin, 500 mg once daily) with or without metronidazole (Flagyl, 500 mg twice daily) for 14 days. An alternative is an initial single dose of ceftriaxone (Rocephin, 250 mg IM), cefoxitin (Mefoxin, 2 g IM plus probenecid 1 g orally), or another parenteral third-generation cephalosporin, followed by doxycycline (100 mg orally twice daily) with or without metronidazole for 14 days. Quinolones are not recommended to treat gonorrhea acquired in California or Hawaii. If the patient may have acquired the disease in Asia, Hawaii, or California, cefixime or ceftriaxone should be used.

**2.** Another alternative is azithromycin (Zithromax, 1 g PO for Chlamydia coverage) and amoxicillin-clavulanate (Amoxicillin, 875 mg PO) once by directly observed therapy, followed by amoxicillin-clavulanate (Amoxicillin, 875 mg PO BID) for 7 to 10 days.

**C. Inpatient therapy**

**1.** For inpatient treatment, the CDC suggests either of the following regimens:

**a. Cefotetan (Cefotan)**, 2 g IV Q12h, or cefoxitin (Mefoxin, 2 g IV Q6h) plus doxycycline (100 mg IV or PO Q12h)

**b. Clindamycin (Cleocin)**, 900 mg IV Q8h, plus gentamicin (1-1.5 mg/kg IV q8h)

**2. Alternative regimens:**

**a. Ofloxacin (Floxin)**, 400 mg IV Q12h or levofloxacin (Levaquin, 500 mg IV QD) with or without metronidazole (Flagyl, 500 mg IV Q8h). Quinolones are not recommended to treat gonorrhea acquired in California or Hawaii. If the patient may have acquired the disease in Asia, Hawaii, or California, cefixime or ceftriaxone should be used.

**b. Ampicillin-sulbactam (Unasyn)**, 3 g IV Q6h plus doxycycline (100 mg IV or PO Q12h)

**3.** Parenteral administration of antibiotics should be continued for 24 hours after clinical response, followed by doxycycline (100 mg PO BID) or clindamycin (Cleocin, 450 mg PO QID) for a total of 14 days.

**4. The following regimen may also be used: Levofloxacin (Levaquin)**, 500 mg IV Q24h, plus metronidazole (Flagyl, 500 mg IV Q8h). With this regimen, azithromycin (Zithromax, 1 g PO once) should be given as soon as the patient is tolerating oral intake. Parenteral therapy is continued until the pelvic tenderness on bimanual examination is mild or absent.

**D. Annual screening** is recommended for all sexually active women under age 25 and for women over 25 if they have new or multiple sexual partners. A retest for chlamydia should be completed in 3 to 4 months after chlamydia treatment because of high rates of reinfection.

**E. Additional evaluation:**

**1.** Serology for the human immunodeficiency virus (HIV)

**2.** Papanicolaou smear

**3.** Hepatitis B surface antigen determination and initiation of the vaccine series for patients who are antigen negative and unvaccinated

**4.** Hepatitis C virus serology

**5.** Serologic tests for syphilis

**References:** See page 255.

## Sexually Transmissible Infections

Approximately 12 million patients are diagnosed with a sexually transmissible infection (STI) annually in the United States. Sequella of STIs include infertility, chronic pelvic pain, ectopic pregnancy, and other adverse pregnancy outcomes.

**Diagnosis and Treatment of Bacterial Sexually Transmissible Infections**

| Organism | Diagnostic Methods | Recommended Treatment | Alternative |
|---|---|---|---|
| Chlamydia trachomatis | Direct fluorescent antibody, enzyme immunoassay, DNA probe, cell culture, DNA amplification | Doxycycline 100 mg PO 2 times a day for 7 days or Azithromycin (Zithromax) 1 g PO | Ofloxacin (Floxin) 300 mg PO 2 times a day for 7 days |
| Neisseria gonorrhoeae | Culture DNA probe | Ceftriaxone (Rocephin) 125 mg IM or Cefixime 400 mg PO or Ciprofloxacin (Cipro) 500 mg PO or Ofloxacin (Floxin) 400 mg PO plus Doxycycline 100 mg 2 times a day for 7 days or azithromycin 1 g PO | Levofloxacin (Levaquin) 250 mg PO once Spectinomycin 2 g IM once |
| Treponema pallidum | Clinical appearance Dark-field microscopy Nontreponemal test: rapid plasma reagin, VDRL Treponemal test: MHA-TP, FTA-ABS | Primary and secondary syphilis and early latent syphilis (<1 year duration): benzathine penicillin G 2.4 million units IM in a single dose. | Penicillin allergy in patients with primary, secondary, or early latent syphilis (<1 year of duration): doxycycline 100 mg PO 2 times a day for 2 weeks. |

**Diagnosis and Treatment of Viral Sexually Transmissible Infections**

| Organism | Diagnostic Methods | Recommended Treatment Regimens |
|---|---|---|
| Herpes simplex virus | Clinical appearance Cell culture confirmation | First episode: Acyclovir (Zovirax) 400 mg PO 5 times a day for 7-10 days, or famciclovir (Famvir) 250 mg PO 3 times a day for 7-10 days, or valacyclovir (Valtrex) 1 g PO 2 times a day for 7-10 days.<br>Recurrent episodes: acyclovir 400 mg PO 3 times a day for 5 days, or 800 mg PO 2 times a day for 5 days or famciclovir 125 mg PO 2 times a day for 5 days, or valacyclovir 500 mg PO 2 times a day for 5 days<br>Daily suppressive therapy: acyclovir 400 mg PO 2 times a day, or famciclovir 250 mg PO 2 times a day, or valacyclovir 250 mg PO 2 times a day, 500 mg PO 1 time a day, or 1000 mg PO 1 time a day |
| Human papilloma virus | Clinical appearance of condyloma papules Cytology | External warts: Patient may apply podofilox 0.5% solution or gel 2 times a day for 3 days, followed by 4 days of no therapy, for a total of up to 4 cycles, or imiquimod 5% cream at bedtime 3 times a week for up to 16 weeks. Cryotherapy with liquid nitrogen or cryoprobe, repeat every 1-2 weeks; or podophyllin, repeat weekly; or TCA 80-90%, repeat weekly; or surgical removal.<br>Vaginal warts: cryotherapy with liquid nitrogen, or TCA 80-90%, or podophyllin 10-25% |
| Human immunodeficiency virus | Enzyme immunoassay Western blot (for confirmation) Polymerase chain reaction | Antiretroviral agents |

**Treatment of Pelvic Inflammatory Disease**

| Regimen | Inpatient | Outpatient |
|---|---|---|
| A | Cefotetan (Cefotan) 2 g IV q12h; or cefoxitin (Mefoxin) 2 g IV q6h plus doxycycline 100 mg IV or PO q12h. | Ofloxacin (Floxin) 400 mg PO bid for 14 days plus metronidazole 500 mg PO bid for 14 days. |

| Regimen | Inpatient | Outpatient |
|---|---|---|
| B | Clindamycin 900 mg IV q8h plus gentamicin loading dose IV or IM (2 mg/kg of body weight), followed by a maintenance dose (1.5 mg/kg) q8h. | Ceftriaxone (Rocephin) 250 mg IM once; or cefoxitin 2 g IM plus probenecid 1 g PO; or other parenteral third-generation cephalosporin (eg, ceftizoxime, cefotaxime) plus doxycycline 100 mg PO bid for 14 days. |

**I.Chlamydia Trachomatis**

**A.**Chlamydia trachomatis is the most prevalent STI in the United States. Chlamydial infections are most common in women age 15-19 years.

**B.**Routine screening of asymptomatic, sexually active adolescent females undergoing pelvic examination is recommended. Annual screening should be done for women age 20-24 years who are either inconsistent users of barrier contraceptives or who acquired a new sex partner or had more than one sexual partner in the past 3 months.

**II.Gonorrhea.** Gonorrhea has an incidence of 800,000 cases annually. Routine screening for gonorrhea is recommended among women at high risk of infection, including prostitutes, women with a history of repeated episodes of gonorrhea, women under age 25 years with two or more sex partners in the past year, and women with mucopurulent cervicitis.

**III.Syphilis**

**A.**Syphilis has an incidence of 100,000 cases annually. The rates are highest in the South, among African Americans, and among those in the 20- to 24-year-old age group.

**B.**Prostitutes, persons with other STIs, and sexual contacts of persons with active syphilis should be screened.

**IV.Herpes simplex virus and human papillomavirus**

**A.**An estimated 200,000-500,000 new cases of herpes simplex occur annually in the United States. New infections are most common in adolescents and young adults.

**B.**Human papillomavirus affects about 30% of young, sexually active individuals.

**References:** See page 255.

## Vaginitis

Approximately 8-18% of women reported an episode of vaginal symptoms in the previous year. The etiology of vaginal complaints includes infection of the vagina, cervix, and upper genital tract, chemicals or irritants (eg, spermicides or douching), hormone deficiency, and rarely systemic diseases.

**I.Clinical evaluation**

**A.**Symptoms of vaginitis include vaginal discharge, pruritus, irritation, soreness, odor, dyspareunia and dysuria. Dyspareunia is a common feature of atrophic vaginitis. Abdominal pain is suggestive of pelvic inflammatory disease and suprapubic pain is suggestive of cystitis.

**B.**A new sexual partner increases the risk of acquiring sexually transmitted diseases, such as trichomonas, chlamydia, or Neisseria gonorrheae. Trichomoniasis often occurs during or immediately after the menstrual period; candida vulvovaginitis often occurs during the premenstrual period.

**C.**Antibiotics and high-estrogen oral contraceptive pills may predispose to candida vulvovaginitis; increased physiologic discharge can occur with oral contraceptives; pruritus unresponsive to antifungal agents suggests vulvar dermatitis.

**II.Physical examination**

**A.**The vulva usually appears normal in bacterial vaginosis. Erythema, edema, or fissure formation suggest candidiasis, trichomoniasis, or dermatitis. Trichomonas is associated with a purulent discharge; candidiasis is associated with a thick, adherent, "cottage cheese-like" discharge; and bacterial vaginosis is associated with a thin, homogeneous, "fishy smelling" discharge. The cervix in women with cervicitis is usually erythematous and friable, with a mucopurulent discharge. Abdominal or cervical motion tenderness is suggestive of PID.

**III.Diagnostic studies**

**A.Vaginal pH.** Measurement of vaginal pH should always be determined. The pH of the normal vaginal secretions is 4.0 to 4.5. A pH above 4.5 suggests bacterial vaginosis or trichomoniasis (pH 5 to 6), and helps to exclude candida vulvovaginitis (pH 4 to 4.5).

**B.Saline microscopy** should look for candidal buds or hyphae, motile trichomonads, epithelial cells studded with adherent coccobacilli (clue cells), and polymorphonuclear cells (PMNs). The addition of 10% potassium hydroxide to the wet mount is helpful in diagnosing candida vaginitis. Culture for candida and trichomonas may be useful if microscopy is negative.

**C.Cervical culture.** A diagnosis of cervicitis, typically due to Neisseria gonorrhoeae or Chlamydia trachomatis, must always be considered in women with purulent vaginal discharge. The presence of high-risk behavior or any sexually transmitted disease requires screening for HIV, hepatitis B, and other STDs.

**Clinical Manifestations of Vaginitis**

| | |
|---|---|
| **Candidal Vaginitis** | Nonmalodorous, thick, white, "cottage cheese-like" discharge that adheres to vaginal walls<br>Hyphal forms or budding yeast cells on wet-mount<br>Pruritus<br>Normal pH (<4.5) |
| **Bacterial Vaginosis** | Thin, dark or dull grey, homogeneous, malodorous discharge that adheres to the vaginal walls<br>Elevated pH level (>4.5)<br>Positive KOH (whiff test)<br>Clue cells on wet-mount microscopic evaluation |
| **Trichomonas Vaginalis** | Copious, yellow-gray or green, homogeneous or frothy, malodorous discharge<br>Elevated pH level (>4.5)<br>Mobile, flagellated organisms and leukocytes on wet-mount microscopic evaluation<br>Vulvovaginal irritation, dysuria |
| **Atrophic Vaginitis** | Vaginal dryness or burning |

**IV.Bacterial vaginosis**

**A.Incidence.** Bacterial vaginosis is the most common cause of vaginitis in women of childbearing age, with prevalence of 5-60%.

**B.Microbiology and risk factors.** Bacterial vaginosis represents a change in vaginal flora characterized by a reduction of lactobacilli and an increase of Gardnerella vaginalis, Mobiluncus species, Mycoplasma hominis, anaerobic gram-negative rods, and Peptostreptococcus species. Risk factors for bacterial vaginosis include multiple or new sexual partners, early age of first coitus, douching, cigarette smoking, and use of an intrauterine contraceptive device.

**C.Clinical features.** Symptoms include a “fishy smelling” discharge that is more noticeable after unprotected intercourse. The discharge is off-white, thin, and homogeneous. Pruritus and inflammation are absent.

**D.Complications**

**1.**Pregnant women appear to be at higher risk of preterm delivery.

**2.**Bacterial vaginosis may cause plasma-cell endometritis, postpartum fever, post-hysterectomy vaginal-cuff cellulitis, and postabortal infection.

**3.**Bacterial vaginosis is a risk factor for HIV acquisition and transmission.

**E.Diagnosis.** Three of the four criteria listed below are necessary for diagnosis.

**1.**Homogeneous, grayish-white discharge

**2.**Vaginal pH greater than 4.5

**3.**Positive whiff-amine test, defined as the presence of a fishy odor when 10% KOH is added to vaginal discharge samples

**4.**Clue cells on saline wet mount (epithelial cells studded with coccobacilli)

**F.Therapy.** Treatment is indicated in women with symptomatic infection and those with asymptomatic infection prior to abortion or hysterectomy.

**1.**Metronidazole or clindamycin administered either orally or intravaginally will result in a high rate of clinical cure (70-80% at 4 weeks of follow-up). Oral medication is more convenient, but associated with a higher rate of systemic side effects than vaginal administration.

**2.**The oral regimen is 500 mg twice daily for 7 days. Topical vaginal therapy with 0.75% metronidazole gel (MetroGel, 5 g once daily for 5 days) is as effective as oral metronidazole.

**3.**Single-dose therapy with 2 g of metronidazole achieves a similar immediate rate of clinical response and is considered an alternative, slightly less effective regimen.

**4.**Side effects of metronidazole include a metallic taste, nausea, a disulfiram-like effect with alcohol, interaction with warfarin, and peripheral neuropathy.

**5.**Topical vaginal therapy with 2% clindamycin cream (5 g once daily for 7 days) appears to be less effective than the metronidazole regimens but is a reasonable choice. Pseudomembranous colitis has been reported with topical clindamycin. Clindamycin cream should not be used with condoms, which may be weakened.

**G.Relapse**

**1.**Approximately 30% of patients have a recurrence within three months. Recurrence usually reflects a failure to eradicate the offending organisms. Management of symptomatic relapse includes prolonged therapy for 10 to 14 days.

**2.**Most women with a history of recurrent infection benefit from suppressive therapy with metronidazole gel 0.75% for 10 days, followed by twice-weekly applications for three to six months.

**V.Candida vulvovaginitis**

**A.Incidence.** Candida vulvovaginitis accounts for one-third of vaginitis. Up to 75% of women report having had at least one episode of candidiasis. The condition is rare before menarche. It is less common in postmenopausal women, unless they are taking estrogen replacement therapy.

**B.Microbiology and risk factors.** Candida albicans is responsible for 80-92% of vulvovaginal candidiasis. Sporadic attacks of vulvovaginal candidiasis usually occur without an identifiable precipitating factor.

**1.Antibiotics.** A minority of women are prone to vulvovaginal candidiasis while taking antibiotics.

**2.Intrauterine devices** have been associated with vulvovaginal candidiasis.

**3.Pregnancy.** Symptomatic infection is more common in pregnancy.

**C.Clinical features.** Vulvar pruritus is the dominant feature. Women may also complain of dysuria (external rather than urethral), soreness, irritation, and dyspareunia. There is often little or no discharge; that which is present is typically white and clumpy. Physical examination often reveals

erythema of the vulva and vaginal mucosa. The discharge is thick, adherent, and "cottage cheese-like."

**D.Diagnosis**

**1.**The vaginal pH is typically 4 to 4.5, which distinguishes candidiasis from Trichomonas or bacterial vaginosis. The diagnosis is confirmed by finding the organism on a wet mount; adding 10% potassium hydroxide facilitates recognition of budding yeast and hyphae. Microscopy is negative in 50% of patients with vulvovaginal candidiasis.

**2.**Empiric therapy is often considered in women with typical clinical features, a normal vaginal pH, and no other pathogens visible on microscopy. Culture should be performed in patients with persistent or recurrent symptoms.

**E.Therapy**

**1.**Women with mild infection usually respond to treatment within a couple of days. More severe infections require a longer course of therapy and may take up to 14 days to fully resolve.

**2.Uncomplicated infection.** Both oral and topical antimycotic drugs achieve comparable clinical cure rates that are in excess of 80%.

**3.**Oral azole agents are more convenient. Side effects of single-dose fluconazole (150 mg) tend to be mild and infrequent, including gastrointestinal intolerance, headache, and rash.

**Treatment regimens for yeast vaginitis***

**1-day regimens**
Clotrimazole vaginal tablets (Mycelex G), 500 mg hs**
Fluconazole tablets (Diflucan), 150 mg PO
Itraconazole capsules (Sporanox), 200 mg PO bid
Tioconazole 6.5% vaginal ointment (Vagistat-1), 4.6 g hs** [5 g]

**3-day regimens**
Butoconazole nitrate 2% vaginal cream (Femstat 3), 5 g hs [28 g]
Clotrimazole vaginal inserts (Gyne-Lotrimin 3), 200 mg hs**
Miconazole vaginal suppositories (Monistat 3), 200 mg hs**
Terconazole 0.8% vaginal cream (Terazol 3), 5 g hs
Terconazole vaginal suppositories (Terazol 3), 80 mg hs
Itraconazole capsules (Sporanox), 200 mg PO qd (4)

**5-day regimen**
Ketoconazole tablets (Nizoral), 400 mg PO bid (4)

**7-day regimens**
Clotrimazole 1% cream (Gyne-Lotrimin, Mycelex-7, Sweet'n Fresh Clotrimazole-7), 5 g hs**
Clotrimazole vaginal tablets (Gyne-Lotrimin, Mycelex-7, Sweet'n Fresh Clotrimazole-7), 100 mg hs**
Miconazole 2% vaginal cream (Femizol-M, Monistat 7), 5 g hs**
Miconazole vaginal suppositories (Monistat 7), 100 mg hs**
Terconazole 0.4% vaginal cream (Terazol 7), 5 g hs

**14-day regimens**
Nystatin vaginal tablets (Mycostatin), 100,000 U hs
Boric acid No. 0 gelatin vaginal suppositories, 600 mg bid (2)

*Suppositories can be used if inflammation is predominantly vaginal; creams if vulvar; a combination if both. Cream-suppository combination packs available: clotrimazole (Gyne-Lotrimin, Mycelex); miconazole (Monistat, M-Zole). If diagnosis is in doubt, consider oral therapy to avoid amelioration of symptoms with use of creams. Use 1-day or 3-day regimen if compliance is an issue. Miconazole nitrate may be used during pregnancy.

**Nonprescription formulation. If nonprescription therapies fail, use terconazole 0.4% cream or 80-mg suppositories at bedtime for 7 days.

**4.Complicated infections.** Factors that predispose to complicated infection include uncontrolled diabetes, immunosuppression, and a history of recurrent vulvovaginal candidiasis. Women with severe inflammation or complicated infection require seven to 14 days of topical therapy or two doses of oral therapy 72 hours apart.

**Management options for complicated or recurrent yeast vaginitis**

Extend any 7-day regimen to 10 to 14 days
Eliminate use of nylon or tight-fitting clothing
Consider discontinuing oral contraceptives
Consider eating 8 oz yogurt (with Lactobacillus acidophilus culture) per day
Improve glycemic control in diabetic patients
For long-term suppression of recurrent vaginitis, use ketoconazole, 100 mg (1/2 of 200-mg tablet) qd for 6 months

**5.Partner treatment** is not necessary since this is not a primary route of transmission.

**6.Pregnancy.** Topical azoles applied for seven days are recommended for treatment during pregnancy.

**F.Women with recurrent infections should receive longer initial therapy** (10 to 14 days of a topical agent or fluconazole 150 mg orally with a repeat dose three days later). Antifungal maintenance suppressive therapy that should be taken for six months after an initial induction regimen include ketoconazole (100 mg per day), itraconazole (100 mg per day or 400 mg once monthly), fluconazole (100 to 150 mg once per week), and clotrimazole (500 mg vaginal suppository once per week). Alternatively, fluconazole 200 mg orally may be given every three days until the patient is asymptomatic, with redosing weekly, tapered to every two weeks, and then every three to four weeks. Redosing once per month just before menses may be effective because this is when most patients flare. Patients receiving long-term ketoconazole should be monitored for hepatotoxicity.

## VI.Trichomoniasis

**A.**Trichomoniasis, the third most common cause of vaginitis, is caused by the flagellated protozoan, Trichomonas vaginalis. The disorder is virtually always sexually transmitted.

**B.Clinical features.** Trichomoniasis in women ranges from an asymptomatic state to a severe, acute, inflammatory disease. Signs and symptoms include a purulent, malodorous, thin discharge (70%) with associated burning, pruritus, dysuria, and dyspareunia. Physical examination reveals erythema of the vulva and vaginal mucosa; the classic green-yellow frothy discharge is observed in 10-30%. Punctate hemorrhages may be visible on the vagina and cervix in 2%.

**C.Complications.** Infection is associated with premature rupture of the membranes and prematurity; however, treatment of asymptomatic infection has not been shown to reduce these complications. Trichomoniasis is a risk factor for development of post-hysterectomy cellulitis. The infection facilitates transmission of the human immunodeficiency virus.

**D.Diagnosis**

**1.**The presence of motile trichomonads on wet mount is diagnostic of infection, but this occurs in only 50-70% of cases. Other findings include an elevated vaginal pH (>4.5) and an increase in polymorphonuclear leukocytes on saline microscopy.

**2.**Culture on Diamond's medium has a 95% high sensitivity and should be considered in patients with elevated vaginal pH, increased numbers of polymorphonuclear leukocytes, and an absence of motile trichomonads and clue cells; rapid diagnostic kits using DNA probes and monoclonal antibodies have a sensitivity of 90%.

**3.**Trichomonads are often seen on conventional Papanicolaou smears, but false positive results are not uncommon (30%). Thus, asymptomatic women with Trichomonas identified on conventional Pap smear should not be treated until the diagnosis is confirmed by wet mount. Treatment of asymptomatic women with trichomonads noted on liquid-based cervical cytology is recommended.

**E.Therapy** is indicated in all nonpregnant women diagnosed with Trichomonas vaginitis and their sexual partner(s). Intercourse should not resume until both partners have completed treatment.

**1.**Metronidazole is the treatment of choice. Oral is preferred to local vaginal therapy since systemic administration achieves therapeutic drug levels in the urethra and periurethral glands. Sexual partners should also be treated.

**2.**Similar cure rates are obtained with oral metronidazole in a dose of 500 mg twice a day for seven days (cure rate, 85-90%) and a single 2 g oral dose (82-88%). Patients should be advised not to take alcohol for the duration of 48 hours after treatment because of the disulfiram-like (Antabuse effect) reaction.

| **Treatment options for trichomoniasis** |
|---|
| **Initial measures**<br>Metronidazole (Flagyl, Protostat), 2 g PO in a single dose, or metronidazole, 500 mg PO bid X 7 days, or metronidazole, 375 mg PO bid X 7 days<br>Treat male sexual partners |
| **Measures for treatment failure**<br>Treatment sexual contacts<br>Re-treat with metronidazole, 500 mg PO bid X 7 days<br>If infection persists, confirm with culture and re-treat with metronidazole,<br>2-4 g PO qd X 3-10 days |

**3.Pregnancy.** Metronidazole is the drug of choice in pregnancy. Metronidazole 500 mg twice daily for 5-7 days is preferred to the 2 g single-dose regimen, but both regimens are acceptable. Treatment of asymptomatic infections is not recommended during pregnancy because it does not prevent preterm delivery.

**4.Refractory cases.** If treatment failure occurs, retreatment with metronidazole (500 mg PO twice a day for seven days) is recommended. If treatment failure recurs again, the woman should be treated with a single oral 2 g dose of oral metronidazole daily for 3-5 days.

## VII.Other causes of vaginitis and vaginal discharge

**A.Atrophic vaginitis**

**1.**Reduced endogenous estrogen causes thinning of the vaginal epithelium. Symptoms include vaginal soreness, postcoital burning, dyspareunia, and occasional spotting. The vaginal mucosa is thin with diffuse erythema, occasional petechiae or ecchymoses, and few or no vaginal folds. There may be a serosanguineous or watery discharge with a pH of 5.0-7.0.

**2.**Treatment consists of topical vaginal estrogen. **Vaginal ring estradiol (Estring)**, a silastic ring impregnated with estradiol, is the preferred means of delivering estrogen to the vagina. The silastic ring delivers 6 to 9 µg of estradiol to the vagina daily. The rings are changed once every three months. Concomitant progestin therapy is not necessary.

**3.Conjugated estrogens (Premarin)**, 0.5 gm of cream, or one-eighth of an applicatorful daily into the vagina for three weeks, followed by twice weekly thereafter is also effective. Concomitant progestin therapy is not necessary.

**4.Estrace cream (estradiol)** can also by given by vaginal applicator at a dose of one-eighth of an applicator or 0.5 g (which contains 50 µg of estradiol) daily into the vagina for three weeks, followed by twice weekly thereafter. Concomitant progestin therapy is not necessary.

**5.Oral estrogen (Premarin)** 0.3 mg qd should also provide relief.

**B.Desquamative inflammatory vaginitis**

**1.**Chronic purulent vaginitis usually occurs perimenopausally, with diffuse exudative vaginitis, massive vaginal-cell exfoliation, purulent vaginal discharge, and occasional vaginal and cervical spotted rash. Laboratory findings included an elevated pH, increased numbers of parabasal cells, the absence of gram-positive bacilli and their replacement by gram-positive cocci on Gram staining. Clindamycin 2% cream is usually effective.

**C.Noninfectious vaginitis and vulvitis**

**1.**Noninfectious causes of vaginitis include irritants (eg, minipads, spermicides, povidone-iodine, topical antimycotic drugs, soaps and perfumes) and contact dermatitis (eg, latex condoms and antimycotic creams).

**2.**Typical symptoms, including pruritus, irritation, burning, soreness, and variable discharge, are most commonly confused with acute candida vaginitis. The diagnosis should be suspected in symptomatic women who do not have an otherwise apparent infectious cause.

**3.**Management of noninfectious vaginitis includes identifying and eliminating the offending agent. Sodium bicarbonate sitz baths and topical vegetable oils may provide some local relief. Topical corticosteroids are not recommended.

**References:** See page 255.

# Urinary Incontinence

Women between the ages of 20 to 80 year have an overall prevalence for urinary incontinence of 53.2 percent.

**I.Types of Urinary Incontinence**

**A.Stress Incontinence**

**1.**Stress incontinence is the involuntary loss of urine produced by coughing, laughing or exercising. The underlying abnormality is typically urethral hypermobility caused by a failure of the anatomic supports of the bladder neck. Loss of bladder neck support is often attributed to injury occurring during vaginal delivery.

**2.**The lack of normal intrinsic pressure within the urethra--known as intrinsic urethral sphincter deficiency--is another factor leading to stress incontinence. Advanced age, inadequate estrogen levels, previous vaginal surgery and certain neurologic lesions are associated with poor urethral sphincter function.

**B.Overactive Bladder.** Involuntary loss of urine preceded by a strong urge to void, whether or not the bladder is full, is a symptom of the condition commonly referred to as "urge incontinence." Other commonly used terms such as detrusor instability and detrusor hyperreflexia refer to involuntary detrusor contractions observed during urodynamic studies.

**II.History and Physical Examination**

**A.**A preliminary diagnosis of urinary incontinence can be made on the basis of a history, physical examination and a few simple office and laboratory tests.

**B.**The medical history should assess diabetes, stroke, lumbar disc disease, chronic lung disease, fecal impaction and cognitive impairment. The obstetric and gynecologic history should include gravity; parity; the number of vaginal, instrument-assisted and cesarean deliveries; the time interval between deliveries; previous hysterectomy and/or vaginal or bladder surgery; pelvic radiotherapy; trauma; and estrogen status.

**Key Questions in Evaluating Patients for Urinary Incontinence**

Do you leak urine when you cough, laugh, lift something or sneeze? How often?
Do you ever leak urine when you have a strong urge on the way to the bathroom? How often?
How frequently do you empty your bladder during the day?
How many times do you get up to urinate after going to sleep? Is it the urge to urinate that wakes you?
Do you ever leak urine during sex?
Do you wear pads that protect you from leaking urine? How often do you have to change them?
Do you ever find urine on your pads or clothes and were unaware of when the leakage occurred?
Does it hurt when you urinate?
Do you ever feel that you are unable to completely empty your bladder?

| Drugs That Can Influence Bladder Function | |
|---|---|
| **Drug** | **Side effect** |
| Antidepressants, antipsychotics, sedatives/hypnotics | Sedation, retention (overflow) |
| Diuretics | Frequency, urgency (OAB) |
| Caffeine | Frequency, urgency (OAB) |
| Anticholinergics | Retention (overflow) |
| Alcohol | Sedation, frequency (OAB) |
| Narcotics | Retention, constipation, sedation (OAB and overflow) |
| Alpha-adrenergic blockers | Decreased urethral tone (stress incontinence) |
| Alpha-adrenergic agonists | Increased urethral tone, retention (overflow) |
| Beta-adrenergic agonists | Inhibited detrusor function, retention (overflow) |

**C.**Because fecal impaction has been linked to urinary incontinence, a history that includes frequency of bowel movements, length of time to evacuate and whether the patient must splint her vagina or perineum during defecation should be obtained. Patients should be questioned about fecal incontinence.

**D.**A complete list of all prescription and nonprescription drugs should be obtained. When appropriate, discontinuation of these medications associated with incontinence or substitution of appropriate alternative medications will often cure or significantly improve urinary incontinence.

**E.Physical Examination**

**1.**Immediately before the physical examination, the patient should void as normally and completely as possible. The voided volume should be recorded. A post-void residual volume can then be determined within 10 minutes by catheterization or ultrasound examination. Post-void residual volumes more than 100 mL are considered abnormal.

**2.**A clean urine sample can be sent for culture and urinalysis.

**3.**Determining post-void residual volume and urinalysis allows screening for overflow incontinence, chronic urinary tract infections, hematuria, diabetes, kidney disease and metabolic abnormalities.

**4.**The abdominal examination should rule out diastasis recti, masses, ascites and organomegaly. Pulmonary and cardiovascular assessment may be indicated to assess control of cough or the need for medications such as diuretics.

**5.**The lumbosacral nerve roots should be assessed by checking deep tendon reflexes, lower extremity strength, sharp/dull sensation and the bulbocavernosus and clitoral sacral reflexes.

**6.**The pelvic examination should include an evaluation for inflammation, infection and atrophy. Signs of inadequate estrogen levels are thinning and paleness of the vaginal epithelium, loss of rugae, disappearance of the labia minora and presence of a urethral caruncle.

**7.**A urethral diverticula is usually identified as a distal bulge under the urethra. Gentle massage of the area will frequently produce a purulent discharge from the urethral meatus.

**8.**Testing for stress incontinence is performed by asking the patient to cough vigorously while the examiner watches for leakage of urine.

**9.**While performing the bimanual examination, levator ani muscle function can be evaluated by asking the patient to tighten her “vaginal muscles” and hold the contraction as long as possible. It is normal for a woman to be able to hold such a contraction for five to 10 seconds. The bimanual examination should also include a rectal examination to assess anal sphincter tone, fecal impaction, occult blood, or rectal lesions.

**III.Treatment of urinary incontinence**

**A.**Rehabilitation of the pelvic floor muscles is the common goal of treatments through the use of pelvic muscle exercises (Kegel's exercises), weighted vaginal cones and pelvic floor electrical stimulation.

**B.**A set of specially designed vaginal weights can be used as mechanical biofeedback to augment pelvic muscle exercises. The weights are held inside the vagina by contracting the pelvic muscles for 15 minutes at a time.

**C.**Pelvic floor electrical stimulation with a vaginal or anal probe produces a contraction of the levator ani muscle. Cure or improvement in 48 percent of treated patients, compared with 13 percent of control subjects.

**D.**Occlusive devices, such as pessaries, can mimic the effects of a retropubic urethropexy. A properly fitted pessary prevents urine loss during vigorous coughing in the standing position with a full bladder.

**E.**Medications such as estrogens and alpha-adrenergic drugs may also be effective in treating women with stress incontinence. Stress incontinence may be treated with localized estrogen replacement therapy (ERT). Localized ERT can be given in the form of estrogen cream or an estradiol-impregnated vaginal ring (Estring).

| Medications Used to Treat Urinary Incontinence | |
|---|---|
| **Drug** | **Dosage** |
| **Stress Incontinence** | |
| Pseudoephedrine (Sudafed) | 15 to 30 mg, three times daily |
| Vaginal estrogen ring (Estring) | Insert into vagina every three months. |
| Vaginal estrogen cream | 0.5 g, apply in vagina every night |
| **Overactive bladder** | |
| Oxybutynin transdermal (Oxytrol) | 39 $cm^2$ patch 2 times/week |
| Oxybutynin ER (Ditropan XL) | 5 to 15 mg, every morning |
| Tolterodine LA (Detrol LA) | 2-4 mg qd |
| Generic oxybutynin | 2.5 to 10 mg, two to four times daily |
| Tolterodine (Detrol) | 1 to 2 mg, two times daily |
| Imipramine (Tofranil) | 10 to 75 mg, every night |
| Dicyclomine (Bentyl) | 10 to 20 mg, four times daily |
| Hyoscyamine (Cystospaz) | 0.375 mg, two times daily |

**F.** Alpha-adrenergic drugs such as pseudoephedrine improve stress incontinence by increase resting urethral tone. These drugs cause subjective improvement in 20 to 60 percent of patients.

**G.** Surgery to correct genuine stress incontinence is a viable option for most patients. Retropubic urethropexies (ie, Burch laparoscopic and Marshall-Marchetti-Krantz [MMK] procedures) and suburethral slings have long-term success rates consistently reported in the 80 to 96 percent range.

**H.** Another minimally invasive procedure for the treatment of stress incontinence caused by intrinsic sphincter deficiency is periurethral injection.

**I. Overactive bladder**

**1.** Behavioral therapy, in the form of bladder retraining and biofeedback, seeks to reestablish cortical control of the bladder by having the patient ignore urgency and void only in response to cortical signals during waking hours.

**2.** Pharmacologic agents may be given empirically to women with symptoms of overactive bladder. Tolterodine (Detrol) and extended-release oxybutynin chloride (Ditropan XL) have largely replaced generic oxybutynin as a first-line treatment option for overactive bladder because of favorable side effect profiles. Oxybutynin transdermal may cause less dry mouth than the oral formulation.

**3.** ERT is also an effective treatment for women with overactive bladder. Even in patients taking systemic estrogen, localized ERT (ie, estradiol-impregnated vaginal ring) may increase inadequate estrogen levels and decrease the symptoms associated with overactive bladder.

**4.** Pelvic floor electrical stimulation is also effective in treating women with overactive bladder. Pelvic floor electrical stimulation results in a 50 percent cure rate of detrusor instability.

**5.** Neuromodulation of the sacral nerve roots through electrodes implanted in the sacral foramina is a promising new surgical treatment that has been found to be effective in the treatment of urge incontinence.

**6.** The FDA has recently approved extracorporeal magnetic innervation, a noninvasive procedure for the treatment of incontinence caused by pelvic floor weakness. Extracorporeal magnetic innervation may have a place in the treatment of women with both stress and urge incontinence.

**References:** See page 255.

## Genital Warts

Genital warts or condyloma acuminata are caused by infection with human papillomavirus (HPV). Types 16, 18, 31, and 45 have been associated strongly with premalignant and malignant cervical carcinoma. About 18% to 33% of sexually active female adolescents test positive for HPV DNA. Common warts are associated with different HPV types than those that cause genital warts.

**I. Symptoms and Signs**

**A.** The lesions of condylomata acuminata are usually flesh- to gray-colored papillomatous growths. They range in size from less than 1 millimeter in diameter to several square centimeters. The presence of koilocytotic cells on Papanicolaou smears from the cervix suggest condyloma.

**B.** Among adolescent and adult males, venereal warts usually are localized to the penis. Lesions present as brown to slate blue pigmented macules and papules.

**II.Treatment**

**A.**Cryotherapy with liquid nitrogen or a cryoprobe is the most effective method of treating single or multiple small lesions. Cryosurgery is more effective than topical therapies. Lesions should be frozen until a 2 mm margin of freeze appears, then allowed to thaw, then refrozen. Repeat freeze several times. Side effects include burning, which resolves within a few hours, and ulceration, which heals in 7 to 10 days with little or no scarring.

**B.**Repeated weekly application of podophyllin as a 10% solution in benzoin has been the principal mode of therapy for many years. Podophyllin can cause chemical burns and neurologic, hematologic, and febrile complications. Podophyllotoxin (podofilox) is more efficacious and less toxic than podophyllin.

**C.**Other treatment modalities include 5-fluorouracil as a 5% cream and a solution of trichloroacetic acid, both of which are painful and can cause ulcers.

**D.Imiquimod (Aldara)** induces interferon. A cream formulation containing 5% imiquimod has resulted in good total clearance rates and tolerable side effects (erythema). The cream is applied three times a week prior to normal sleeping hours and is washed off after 6 to 10 hours with mild soap and water.

**E.**Surgical techniques include conventional surgery, electrocautery, and laser therapy. Intralesional or systemic administration of interferon is effective for recalcitrant disease.

**F.**Sexual transmission of HPV can be decreased by using condoms. Examination of sex partners is unnecessary; most probably are infected with HPV already, and no test for asymptomatic infection is available.

**References:** See page 255.

## Pubic Infections

**I.Molluscum contagiosum**

**A.**This disease is produced by a virus of the pox virus family and is spread by sexual or close personal contact. Lesions are usually asymptomatic and multiple, with a central umbilication. Lesions can be spread by autoinoculation and last from 6 months to many years.

**B.Diagnosis.** The characteristic appearance is adequate for diagnosis, but biopsy may be used to confirm the diagnosis.

**C.Treatment.** Lesions are removed by sharp dermal curette, liquid nitrogen cryosurgery, or electrodesiccation.

**II.Pediculosis pubis (crabs)**

**A.**Phthirus pubis is a blood sucking louse that is unable to survive more than 24 hours off the body. It is often transmitted sexually and is principally found on the pubic hairs. Diagnosis is confirmed by locating nits or adult lice on the hair shafts.

**B.Treatment**

**1.Permethrin cream (Elimite),** 5% is the most effective treatment; it is applied for 10 minutes and washed off.

**2.Kwell shampoo,** lathered for at least 4 minutes, can also be used, but it is contraindicated in pregnancy or lactation.

**3.**All contaminated clothing and linen should be laundered.

**III.Pubic scabies**

**A.**This highly contagious infestation is caused by the Sarcoptes scabiei (0.2-0.4 mm in length). The infestation is transmitted by intimate contact or by contact with infested clothing. The female mite burrows into the skin, and after 1 month, severe pruritus develops. A multiform eruption may develop, characterized by papules, vesicles, pustules, urticarial wheals, and secondary infections on the hands, wrists, elbows, belt line, buttocks, genitalia, and outer feet.

**B.Diagnosis** is confirmed by visualization of burrows and observation of parasites, eggs, larvae, or red fecal compactions under microscopy.

**C.Treatment**. Permethrin 5% cream (Elimite) is massaged in from the neck down and remove by washing after 8 hours.

**References:** See page 255.

# *Urologic Disorders*

## Benign Prostatic Hyperplasia

More than 80 percent of men older than 80 years have benign prostatic hyperplasia (BPH). When symptoms of urinary obstruction interfere with quality of life, treatment is warranted. Sequelae of BPH include urinary retention, detrusor instability, infection, stone formation, bladder diverticula, and upper tract dilation with renal insufficiency.

**I.Clinical evaluation**

**A.Obstructive symptoms**, such as nocturia, a slow urine stream, intermittency, and double voiding, are generally evaluated through focused history taking, and a digital rectal examination, with or without serum PSA testing.

**B.Symptoms of BPH** may be obstructive, which are secondary to bladder outlet obstruction or impaired bladder contractility, or irritative, which result from decreased vesicle compliance and increased bladder instability. Obstructive symptoms include a weak stream, hesitancy, abdominal straining, terminal dribbling, an intermittent stream, and retention; irritative symptoms are frequency, nocturia, urgency, and pain during urination.

**C.Physical examination** should include a digital rectal examination, and a focused neurologic examination to rule out a neurologic cause of symptoms.

**BPH Symptom Score**

For each question, circle the answer that best describes your situation. Add the circled number together to get your total score. See the key at the bottom of this form to determine the overall rating of your symptoms.

| | Not at all | Less than one in five times | Less than half of the time | About half of the time | More than half of the time | Almost always |
|---|---|---|---|---|---|---|
| In the past month, how often have you had a sensation of not emptying your bladder completely after you finished voiding? | 0 | 1 | 2 | 3 | 4 | 5 |
| In the past month, how often have you had to urinate again less than 2 hours after you finished urinating before? | 0 | 1 | 2 | 3 | 4 | 5 |
| In the past month, how often have you found you stopped and started again several times when you urinated? | 0 | 1 | 2 | 3 | 4 | 5 |
| In the past month, how often have you found it difficult to postpone urination? | 0 | 1 | 2 | 3 | 4 | 5 |
| In the past month, how often have you had a weak urinary stream? | 0 | 1 | 2 | 3 | 4 | 5 |
| In the past month, how often have you had to push or strain to begin urination? | 0 | 1 | 2 | 3 | 4 | 5 |
| In the past month, how many times did you typically get up to urinate from the time you went to bed until you arose in the morning? | 0 | 1 | 2 | 3 | 4 | 5 |

**D.Laboratory assessment**

**1.Urinalysis and a serum creatinine assay** are useful to ascertain there is no infection, hematuria, or decreased renal function.

**2.Prostate-specific antigen (PSA)** testing may be offered to patients at risk for prostate cancer who prefer to be screened for the malignancy. PSA testing and rectal examination should be offered annually to men 50 years of age and older if they are expected to live at least 10 more years. Black men and men who have a first-degree relative with prostate cancer are at high risk for prostate cancer. These men should be offered screening at 45 years of age.

**II.Treatment options**

**A.**Watchful Waiting is appropriate in patients with a low AUA symptom score (zero to seven) because studies have shown that medications are not significantly more effective than placebo in these patients.

**B.Medical treatments**

**1.Nonselective alpha-blockers**

**a.**Doxazosin (Cardura), prazosin (Minipress), and terazosin (Hytrin) reduce prostatic smooth muscle tone and, thus, have an immediate effect on urinary flow. These medications quickly improve BPH symptoms.

**b.**Side effects such as dizziness, postural hypotension, fatigue, and asthenia affect from 7 to 9 percent of patients treated with nonselective alpha blockers. Side effects can be minimized by bedtime administration and slow titration of the dosage. Alpha-blockers can be used with other therapies as needed. Prazosin has the cost advantage of generic availability; however, unlike doxazosin and terazosin, it is not available in a once-daily formulation.

**c.**Therapy for BPH with terazosin (Hytrin) is usually begun with a daily dosage of 1 mg hs. Dosage is raised to 2 mg, 5 mg, and 10 mg. Clinical response may not be seen for 4-6 weeks, even at the 10-mg dosage. Doxazosin (Cardura) is usually given at dosages of 1-4 mg qd.

| Starting dosages of alpha-blocking agents for managing benign prostatic hypertrophy | |
|---|---|
| **Drug** | **Starting dosage** |
| Afuzosin (Uroxatral) | 10 mg qd |
| Tamsulosin (Flomax) | 0.4 mg qd |
| Terazosin (Hytrin) | 1 mg qd, adjusted up to 5 mg qd |
| Doxazosin mesylate (Cardura) | 1 mg qd, adjusted up to 4 mg qd |

**2.Selective alpha-blockers**

**a.Tamsulosin (Flomax)** is a highly selective $alpha_{1A}$-adrenergic antagonist that was developed to avoid the side effects of nonselective agents. Some patients who do not respond to nonselective alpha-blockers may respond to tamsulosin and, because of the selectivity, may have fewer side effects, including hypotension. Tamsulosin is initiated in a dosage of 0.4 mg once daily, with a maximum of 0.8 mg per day. Tamsulosin has no antihypertensive effect.

**b.Afuzosin (Uroxatral)** causes less ejaculatory dysfunction than tamsulosin. Dosage is 10 mg qd. Contraindicated in moderate to severe hepatic impairment.

**3.5a-Reductase inhibitors**

**a.Finasteride (Proscan)** slowly induces an 80 to 90 percent reduction in the serum dihydrotestosterone level. As a result, prostatic volume decreases by about 20 percent over three to six months. Improvements with finasteride are significantly less than those with any alpha-blocker or surgery. Finasteride may work best in men with a large gland, whereas alpha-blockers are effective across the range of prostate sizes. Side effects with finasteride are similar to that with placebo, and include decreased libido, ejaculatory disorder, and impotence. The daily dosage is 5 mg.

**b.Dutasteride (Duagen),** 0.5-mg capsule qd, is approved for the treatment of BPH (labeling for male-pattern baldness is pending). This drug has a distinct mechanism of action, in that it blocks both types 1 and 2 5a-reductase. Sexual side effects are similar to those of finasteride.

**C.Surgical treatments**

**1.**Surgery should be considered in patients who fail medical treatment, have refractory urinary retention, fail catheter removal, or have recurrent urinary tract infections, persistent hematuria, bladder stones, or renal insufficiency. Surgery can also be the initial treatment in patients with high AUA symptom scores who want surgical treatment and are good candidates for surgery.

**2.Transurethral resection of the prostate (TURP).** The most commonly employed surgical procedure for BPH, TURP reduces symptoms in 88 percent of patients. The most frequent complications of the procedure are inability to void, clot retention, and secondary infection. Bleeding occurs in only 1 percent of patients. Long-term complications include retrograde ejaculation (70%), impotence (14%), partial incontinence (6%), and total incontinence (1%).

**References:** See page 255.

# Prostatitis

Prostatitis is a common condition, with a 5 percent lifetime prevalence to 9 percent. Prostatitis is divided into three subtypes: acute, chronic bacterial prostatitis and chronic nonbacterial prostatitis/chronic pelvic pain syndrome (CNP/CPPS).

**I.Acute Bacterial Prostatitis**

**A.**Acute bacterial prostatitis (ABP) should be considered a urinary tract infection. The most common cause is Escherichia coli. Other species frequently found include Klebsiella, Proteus, Enterococci and Pseudomonas. On occasion, cultures grow Staphylococcus aureus, Streptococcus faecalis, Chlamydia or Bacteroides species.

**B.**Patients may present with fever, chills, low back pain, perineal or ejaculatory pain, dysuria, urinary frequency, urgency, myalgias and obstruction. The prostate gland is tender and may be warm, swollen, firm and irregular. Vigorous digital examination of the prostate should be avoided because it may induce bacteremia.

**C.**The infecting organism can often be identified by urine culturing.

**D.**Treatment consists of trimethoprim-sulfamethoxazole (TMP-SMX [Bactrim, Septra]), a quinolone or tetracycline. Men at increased risk for sexually transmitted disease require antibiotic coverage for Chlamydia.

| Common Antibiotic Regimens for Acute Bacterial Prostatitis | |
|---|---|
| **Medication** | **Standard dosage** |
| Trimethoprim-sulfamethoxazole (Bactrim, Septra) | 1 DS tablet (160/800 mg) twice a day |
| Doxycycline (Vibramycin) | 100 mg twice a day |

| Medication | Standard dosage |
|---|---|
| Ciprofloxacin (Cipro) | 500 mg twice a day |
| Norfloxacin (Noroxin) | 400 mg twice a day |
| Ofloxacin (Floxin) | 400 mg twice a day |

**E.**Antibiotic therapy should be continued for three to four weeks. Extremely ill patients should be hospitalized to receive a parenteral broad-spectrum cephalosporin and an aminoglycoside.

**II.Chronic Bacterial Prostatitis**

**A.**Chronic bacterial prostatitis (CBP) is a common cause of recurrent urinary tract infections in men. Men experience irritative voiding symptoms, pain in the back, testes, epididymis or penis, low-grade fever, arthralgias and myalgias. Signs may include urethral discharge, hemospermia and secondary epididymo-orchitis. Often the prostate is normal on rectal examination.

**B.**CBP presents with negative premassage urine culture results, and greater than 10 to 20 white blood cells per high-power field in the pre- and the postmassage urine specimen. Significant bacteriuria in the postmassage urine specimen suggests chronic bacterial prostatitis.

**C.**TMP-SMX is the first-line antibiotic for CBP. Norfloxacin (Noroxin) taken twice a day for 28 days achieves a cure rate in 64 percent. Ofloxacin (Floxin) is also highly effective. Some men require long-term antibiotic suppression with TMP-SMX or nitrofurantoin.

**III.Chronic Nonbacterial Prostatitis/Chronic Pelvic Pain Syndrome (Prostatodynia)**

**A.**Patients with CNP/CPPS have painful ejaculation pain in the penis, testicles or scrotum, low back pain, rectal or perineal pain, and/or inner thigh pain. They often have irritative or obstructive urinary symptoms and decreased libido or impotence. The physical examination is usually unremarkable, but patients may have a tender prostate.

**B.**No bacteria will grow on culture, but leukocytosis may be found in the prostatic secretions.

**C.**Treatment begins with 100 mg of doxycycline (Vibramycin) or minocycline (Minocin) twice daily for 14 days. Other therapies may include Allopurinol (Zyloprim), thrice-weekly prostate massage or transurethral microwave thermotherapy.

**D.**Hot sitz baths and nonsteroidal anti-inflammatory drugs (NSAIDs) may provide some relief. Some men may notice aggravation of symptoms with alcohol or spicy foods and should avoid them. Anticholinergic agents (oxybutynin [Ditropan]) or alpha-blocking agents (doxazosin [Cardura], tamsulosin [Flomax] or terazosin [Hytrin]) may be beneficial.

**References:** See page 255.

## Acute Epididymoorchitis

**I.Clinical evaluation of testicular pain**

**A.**Epididymoorchitis is indicated by a unilateral painful testicle and a history of unprotected intercourse, new sexual partner, urinary tract infection, dysuria, or discharge. Symptoms may occur following acute lifting or straining.

**B.**The epididymis and testicle are painful, swollen, and tender. The scrotum may be erythematosus and warm, with associated spermatic cord thickening or penile discharge.

**C.Differential diagnosis of painful scrotal swelling**

**1.**Epididymitis, testicular torsion, testicular tumor, hernia.

**2.**Torsion is characterized by sudden onset, age <20, an elevated testicle, and previous episodes of scrotal pain. The epididymis is usually located anteriorly on either side, and there is an absence of evidence of urethritis and UTI.

**3.**Epididymitis is characterized by fever, laboratory evidence of urethritis or cystitis, and increased scrotal warmth.

**II.Laboratory evaluation of epididymoorchitis**

**A.**Epididymoorchitis is indicated by leukocytosis with a left shift; UA shows pyuria and bacteriuria. Midstream urine culture will reveal gram negative bacilli. Chlamydia and Neisseria cultures should be obtained.

**B.Common pathogens**

**1.Younger men.** Epididymoorchitis is usually associated with sexually transmitted organisms such as Chlamydia and gonorrhea.

**2.Older men.** Epididymoorchitis is usually associated with a concomitant urinary tract infection or prostatitis caused by E. coli, proteus, Klebsiella, Enterobacter, or Pseudomonas.

**III.Treatment of epididymoorchitis**

**A.**Bed rest, scrotal elevation with athletic supporter, an ice pack, analgesics, and antipyretics are prescribed. Sexual and physical activity should be avoided.

**B.Sexually transmitted epididymitis in sexually active males**

**1.**Ceftriaxone (Rocephin) 250 mg IM x 1 dose **AND** doxycycline 100 mg PO bid x 10 days **OR**

**2.**Ofloxacin (Floxin) 300 mg bid x 10 days.

**3.**Treat sexual partners

**C.Epididymitis secondary to urinary tract infection**

**1.**TMP/SMX DS bid for 10 days **OR**

**2.**Ofloxacin (Floxin) 300 mg PO bid for 10 days.

**References:** See page 255.

# Male Sexual Dysfunction

Erectile dysfunction is defined as the persistent inability to achieve or maintain penile erection sufficient for sexual intercourse. Between the ages of 40 and 70 years, the probability of complete erectile dysfunction triples from 5.1 percent to 15 percent.

**I.Physiology of erection**

**A.**Penile erection is mediated by the parasympathetic nervous system, which when stimulated causes arterial dilation and relaxation of the cavernosal smooth muscle. The increased blood flow into the corpora cavernosa in association with reduced venous outflow results in penile rigidity.

**B.**Nitric oxide is a chemical mediator of erection. This substance is released from nerve endings and vascular endothelium, causing smooth muscle relaxation, resulting in venous engorgement and penile tumescence.

**Causes of Erectile Dysfunction and Diagnostic Clues**

| Cause | History | Physical Examination | Possible laboratory findings |
|---|---|---|---|
| Vascular | Coronary artery disease; hypertension; claudication; dyslipidemia; smoking | Decreased pulses; bruits; elevated blood pressure; cool extremities | Abnormal lipid profile<br>Abnormal penile-brachial pressure index |
| Diabetes mellitus | Diabetes; polyuria; polydipsia; polyphagia | Peripheral neuropathy; retinopathy; obesity | Abnormal fasting blood glucose<br>Elevated glycosylated hemoglobin<br>Proteinuria<br>Glycosuria<br>Hypertriglyceridemia |
| Hypogonadism | Decreased libido; fatigue | Bilateral testicular atrophy; scant body hair; gynecomastia | Decreased free testosterone<br>Increased LH<br>Increased FSH |
| Hyperprolactinemia | Decreased libido; galactorrhea; visual complaints; headache | Bitemporal hemianopsia | Elevated prolactin<br>Abnormal CT or MRI scans of pituitary gland |
| Hypothyroidism | Fatigue; cold intolerance | Goiter; myxedema; dry skin; coarse hair | Increased TSH<br>Decreased free $T_4$ |
| Hyperthyroidism | Heat intolerance; weight loss; diaphoresis; palpitations | Lid lag; exophthalmos; hyperreflexia; tremor; tachycardia | Decreased TSH<br>Increased free $T_4$ |
| Cushing's syndrome | Easy bruising; weight gain; corticosteroid use | Truncal obesity; "moon face"; "buffalo hump"; striae | Elevated overnight dexamethasone suppression test |
| Alcoholism | Excessive alcohol use; social, economic or occupational consequences of alcohol abuse; withdrawal symptoms | Positive screen; thin body habitus; palmar erythema; spider telangiectasias; gynecomastia; tremor | Abnormal hepatic transaminases<br>Decreased albumin<br>Macrocytic anemia |
| Neurologic | Spinal cord injury; nerve injury (prostate surgery); stroke; peripheral neuropathy; incontinence; multiple sclerosis; Parkinson's disease | Motor or sensory deficits; aphasia; gait abnormality; abnormal bulbocavernosus reflex; tremor | |
| Mechanical | Genital trauma or surgery; Peyronie's disease; congenital abnormalities | Fibrous penile plaques or chordae | None |

| Cause | History | Physical Examination | Possible laboratory findings |
|---|---|---|---|
| Psychogenic | Nocturnal erections; sudden onset; history of depression; anhedonia; poor relationship with partner; anxiety; life crisis | Sad or withdrawn affect; tearful; psychomotor retardation; depression | Nocturnal penile tumescence (stamp test; Snap-Gauge) |
| Pharmacologic | Inquire about all prescription and nonprescription drugs | | |

**II.Sexual history**

**A.**Abrupt onset of impotency is usually caused by psychogenic impotence. In comparison, men suffering from impotence of any other cause complain of gradual and sporadic onset of impotency at first, then more consistently.

**B.**Most men experience spontaneous erections during REM sleep, and often wake up with an erection, attesting to the integrity of neurogenic reflexes and corpora cavernosae blood flow. Complete loss of nocturnal erections is present in men with neurologic or vascular disease. Nonsustained erection with detumescence after penetration is most commonly due to anxiety or the vascular steal syndrome.

**C.Impotence risk factors** include a history of cigarette smoking, diabetes mellitus, hypertension, alcoholism, drug abuse and depression. Erectile dysfunction is often associated with bicycling, resulting in penile numbness and impotence.

**D.Medications associated with impotence.** Spironolactone, clonidine, guanethidine, methyldopa, thiazide diuretics, most antidepressants, ketoconazole, cimetidine, alcohol, methadone, heroin and cocaine.

**III.Physical examination**

**A.Decreased femoral and peripheral pulses** suggest vasculogenic impotence. The presence of femoral bruits implies possible pelvic blood occlusion.

**B.Visual field defects** may suggest a pituitary tumor. Gynecomastia suggest Klinefelter's syndrome. Penile strictures are indicative of Peyronie's disease. Examination of the testicles may reveal atrophy, asymmetry or masses. The cremasteric reflex assesses the integrity of the thoracolumbar erection center. This is elicited by stroking the inner things and observing ipsilateral contraction of the scrotum.

**IV.Laboratory testing**

**A.Nocturnal penile tumescence testing**

**1.**The Rigi-Scan monitor provides accurately quantifies the number, tumescence and rigidity of erectile episodes a man experiences as he sleeps in his own bed.

**2.**Impotent men with normal NPT are considered to have psychogenic impotence, whereas those with impaired NPT are considered to have “organic” impotence usually due to vascular or neurologic disease. In comparison, testosterone deficient hypogonadal men are still capable of exhibiting some erectile activity during nocturnal penile tumescence studies.

**Agents That May Cause Erectile Dysfunction**

- Antidepressants
  - Monoamine oxidase inhibitors
  - Selective serotonin reuptake inhibitors
  - Tricyclic antidepressants
- Antihypertensives
  - Beta blockers
  - Centrally acting alpha agonists
  - Diuretics
- Antipsychotics
- Anxiolytics
- Miscellaneous
  - Cimetidine (Tagamet)
  - Corticosteroids
  - Finasteride (Proscar)
  - Gemfibrozil (Lopid)
- Drugs of abuse
  - Alcohol
  - Anabolic steroids
  - Heroin
  - Marijuana

**V.Laboratory tests**

**A.**A urinalysis, complete blood count and basic chemistry panel will help to rule out most metabolic and renal diseases. In elderly men, thyroid-stimulating hormone level should be measured to rule out thyroid dysfunction. A free testosterone level should be obtained in all men aged 50 and older and in those younger than 50 who have symptoms or signs of hypogonadism (eg, decreased libido, testicular atrophy, reduced amount of body hair).

**B.**The prolactin level should be measured if the free testosterone level is low, the patient has a substantial loss of libido, or if a prolactinoma is suspected on the basis of a history of headache with visual field cuts. Luteinizing hormone level is reserved for use in distinguishing primary from secondary hypogonadism in men with low testosterone levels.

**VI. Treatment of male sexual dysfunction**

**A. Sildenafil (Viagra)** is effective for a wide range of disorders causing erectile dysfunction.

**1.** A higher percentage of successful sexual intercourse is achieved with sildenafil compared with placebo (57 vs. 21 percent).

**2. Dose.** Sildenafil should be taken orally about one hour before a planned sexual encounter. The initial dose should be 50 mg, and the dosage should be reduced to 25 mg if side effects occur. The dose can be increased to 100 mg. Each sildenafil pill costs $9.00 retail.

**3. Side effects** include headache, lightheadedness, dizziness, flushing, distorted vision, and syncope.

**4. Cardiovascular effects**

**a.** Sildenafil is a vasodilator that lowers the blood pressure by about 8 mm Hg; this change typically produces no symptoms. The combination of sildenafil and nitrates can lead to severe hypotension and syncope. Sildenafil is contraindicated in patients taking nitrates. If a man who has taken sildenafil has an acute ischemic syndrome, nitrates should not be prescribed within 24 hours.

**b.** Sildenafil has been associated with myocardial infarction and sudden death. It does not appear to have adverse effects on coronary hemodynamics. Sildenafil is safe for men with stable coronary artery disease who are not taking nitrates.

**5.** Sildenafil causes blue vision in 3 percent of men, lasting two to three hours. Sildenafil is potentially hazardous in the following:

**a.** Active coronary ischemia (eg, positive exercise test).

**b.** Heart failure and borderline low blood pressure or low volume status.

**c.** Complicated, multidrug, antihypertensive drug regimens.

**d.** Those taking drugs that can prolong the half-life of sildenafil by blocking CYP3A4X.

**6.** Men who are considering sildenafil should be questioned regarding exercise tolerance. Sildenafil can be considered in men who are participating in aerobic activities. If such activity cannot be documented, exercise treadmill testing should be considered.

**B. Vardenafil (Levitra)** is a phosphodiesterase inhibitor, which is similar to sildenafil. The dosage is 10 mg, taken 60 min before sexual activity.

**C. Tadalafil (Cialis)** is a more selective and more potent phosphodiesterase inhibitor than sildenafil, and it has a more rapid onset of action, and a longer duration of action (36 hours) than sildenafil, allowing for more spontaneity in sexual activity. The dosage is 10-20 mg before sexual activity.

**D. Penile self-injection**

**1.** Intrapenile injection therapy with alprostadil (prostaglandin E1, Caverject), papaverine, or alprostadil with papaverine and phentolamine (Tri-Mix) have all been used to induce erection. Firm erection can be expected within a few minutes after intrapenile installation of the drug.

**2. Alprostadil (Caverject)** injection results in satisfactory sexual activity in 87 percent of the men. There is a very high attrition rate.

**3. Side effects.** The major side effect of intrapenile alprostadil therapy is penile pain, occurring in 50 percent. Priapism, or a prolonged erection lasting more than four to six hours, requires immediate urologic attention to evacuate blood clogged within the corpora cavernosae. Prolonged erections occur in 6 to 11%.

**E. Intraurethral alprostadil** (MUSE) provides a less invasive alternative to intrapenile injection. Two-thirds of men respond to intraurethral alprostadil with an erection sufficient for intercourse. Priapism and penile fibrosis were less common than after alprostadil given by penile injection.

**F. Vacuum-assisted erection devices** utilize vacuum pressure to encourage increased arterial inflow and occlusive rings to discourage venous egress. Patients cannot, however, ejaculate externally because the occlusive rings also compress the penile urethra. Vacuum devices create erections in 67 percent. Satisfaction with vacuum-assisted erections has varies between 25 and 49 percent.

**G. Penile prostheses.** Drug and penile injection therapy has greatly reduced reliance on surgical implants of penile prostheses as a treatment for men with erectile dysfunction. This form of therapy remains an option for those men who do not respond to sildenafil and find penile injection or vacuum erection therapy distasteful.

**H. Androgen replacement therapy** requires either injections of long-acting testosterone esters, one of three available testosterone patches, or testosterone gel (Androgel). One patch (Testoderm) is applied once a day to the scrotum. Androderm and Testoderm TTS are applied daily to the torso or extremities. Androgel is applied as one packet once a day to the upper arm, chest, or abdomen.

**VII. Premature ejaculation** is defined as an inability to control ejaculation so that both partners enjoy sexual intercourse. Approximately 20 percent of men complain of premature

ejaculation. Nonpharmacologic therapy such as the "pause and squeeze" technique has achieved variable success, but drug therapy has proved quite useful.

**A.** With Paroxetine (Paxil, 20 mg) three to four hours before planned intercourse, the mean ejaculatory latency time is significantly increased compared with placebo (3.2 versus 0.45 minutes).

**References:** See page 255.

# Psychiatric Disorders

## Depression

The lifetime prevalence of major depression in the United States is 17 percent. In primary care, depression has a prevalence rate of 4.8 to 8.6 percent.

**I.Diagnosis**

**A.**The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) includes nine symptoms in the diagnosis of major depression.

**B.**These nine symptoms can be divided into two clusters: (1) physical or neurovegetative symptoms and (2) psychologic or psychosocial symptoms. The nine symptoms are: depressed mood plus sleep disturbance; interest/pleasure reduction; guilt feelings or thoughts of worthlessness; energy changes/fatigue; concentration/attention impairment; appetite/weight changes; psychomotor disturbances, and suicidal thoughts.

| **Diagnostic Criteria for Major Depression, DSM IV** |
|---|
| **Cluster 1: Physical or neurovegetative symptoms**<br>Sleep disturbance<br>Appetite/weight changes<br>Attention/concentration problem<br>Energy-level change/fatigue<br>Psychomotor disturbance |
| **Cluster 2: Psychologic or psychosocial symptoms**<br>Depressed mood and/or<br>Interest/pleasure reduction<br>Guilt feelings<br>Suicidal thoughts |
| **Note:** Diagnosis of major depression requires at least one of the first two symptoms under cluster 2 and four of the remaining symptoms to be present for at least two weeks. Symptoms should not be accounted for by bereavement. |

**II.Drug Therapy**

| **Characteristics of Common Antidepressants** | | |
|---|---|---|
| **Drug** | **Recommended Dosage** | **Comments** |
| **Selective Serotonin Reuptake Inhibitors (SSRIs)** | | |
| Escitalopram (Lexapro) | 10 mg qd | Minimal sedation, activation, or inhibition of hepatic enzymes, nausea, anorgasmia, headache |
| Citalopram (Celexa) | Initially 20 mg qd; maximum 40 mg/d | |
| Fluoxetine (Prozac) | 10-20 mg qd initially, taken in AM | Anxiety, insomnia, agitation, nausea, anorgasmia, erectile dysfunction, headache, anorexia. |
| Fluvoxamine (LuVox) | 50-100 mg qhs; max 300 mg/d [50, 100 mg] | Headache, nausea, sedation, diarrhea |
| Paroxetine (Paxil) | 20 mg/d initially, given in AM; increase in 10-mg/d increments as needed to max of 50 mg/d. [10, 20, 30, 40 mg] | Headache, nausea, somnolence, dizziness, insomnia, abnormal ejaculation, anxiety, diarrhea, dry mouth. |
| Sertraline (Zoloft) | 50 mg/d, increasing as needed to max of 200 mg/d [50, 100 mg] | Insomnia, agitation, dry mouth, headache, nausea, anorexia, sexual dysfunction. |
| **Secondary Amine Tricyclic Antidepressants** | | |
| Desipramine (Norpramin, generics) | 100-200 mg/d, gradually increasing to 300 mg/d as tolerated.[10, 25, 50, 75, 100, 150 mg] | No sedation; may have stimulant effect; best taken in morning to avoid insomnia. |
| Nortriptyline (Pamelor) | 25 mg tid-qid, max 150 mg/d. [10, 25, 50, 75 mg] | Sedating |

| Drug | Recommended Dosage | Comments |
|---|---|---|
| **Tertiary Amine Tricyclics** | | |
| Amitriptyline (Elavil, generics) | 75 mg/d qhs-bid, increasing to 150-200 mg/d. [25, 50, 75, 100, 150 mg] | Sedative effect precedes antidepressant effect. High anticholinergic activity. |
| Clomipramine (Anafranil) | 25 mg/d, increasing gradually to 100 mg/d; max 250 mg/d; may be given once qhs [25, 50, 75 mg]. | Relatively high sedation, anticholinergic activity, and seizure risk. |
| Protriptyline (Vivactil) | 5-10 mg PO tid-qid; 15-60 mg/d [5, 10 mg] | Useful in anxious depression; nonsedating |
| Doxepin (Sinequan, generics) | 50-75 mg/d, increasing up to 150-300 mg/d as needed [10, 25, 50, 75, 100, 150 mg] | Sedating. Also indicated for anxiety. Contraindicated in patients with glaucoma or urinary retention. |
| Imipramine (Tofranil, generics) | 75 mg/d in a single dose qhs, increasing to 150 mg/d; 300 mg/d. [10, 25, 50 mg] | High sedation and anticholinergic activity. Use caution in cardiovascular disease. |
| **Miscellaneous** | | |
| Bupropion (Wellbutrin, Wellbutrin SR) | 100 mg bid; increase to 100 mg tid [75, 100 mg] Sustained release: 100-200 mg bid [100, 150 mg] | Agitation, dry mouth, insomnia, headache, nausea, constipation, tremor. Good choice for patients with sexual side effects from other agents; contraindicated in seizure disorders. |
| Venlafaxine (Effexor) | 75 mg/d in 2-3 divided doses with food; increase to 225 mg/d as needed. [25, 37.5, 50, 75, 100 mg]. Extended-release: initially 37.5 mg qAM. The dosage can be increased by 75 mg every four days to a max of 225 mg qd [37.5, 75, 100, 150 mg]. | Inhibits norepinephrine and serotonin. Hypertension, nausea, insomnia, dizziness, abnormal ejaculation, headache, dry mouth, anxiety. |
| Maprotiline (Ludiomil) | 75 to 225 in single or divided doses [25, 50, 75 mg]. | Delays cardiac conduction; high anticholinergic activity; contraindicated in seizure disorders. |
| Mirtazapine (Remeron) | 15 to 45 PO qd [15, 30 mg] | High anticholinergic activity; contraindicated in seizure disorders. |
| Nefazodone (Serzone) | Start at 100 mg PO bid, increase to 150-300 mg PO bid as needed [100, 150, 200, 250 mg]. | Headache, somnolence, dry mouth, blurred vision. Postural hypotension, impotence. |
| Reboxetine (Vestra) | 5 mg bid | Selective norepinephrine reuptake inhibitor. Dry mouth, insomnia, constipation, increased sweating |
| Trazodone (Desyrel, generics) | 150 mg/d, increasing by 50 mg/d every 3-4 d 400 mg/d in divided doses [50, 100, 150, 300 mg] | Rarely associated with priapism. Orthostatic hypotension in elderly. Sedating. |

**A.Selective Serotonin Reuptake Inhibitors**

**1.**The selective serotonin reuptake inhibitors (SSRIs) all share the property of blocking the action of serotonin reuptake pump. The antidepressant effects of SSRIs may not appear for three to six weeks.

**2.Fluoxetine (Prozac).**

**a.**Fluoxetine is available generically. The half-life (t 1/2) of fluoxetine is four to six days. Fluoxetine is a potent inhibitor of CYP2D6. Drugs metabolized by hepatic CYP2D6 (tricyclics, antiarrhythmics) must be used cautiously when coadministered with fluoxetine.

**b.**The usual effective dose of fluoxetine is 20 mg QD. The dosage can be increased by 10 to 20 mg as tolerated up to 80 mg QD.

**c.Once weekly fluoxetine** (Prozac) can be administered for patients who have responded to the daily fluoxetine preparation. Patients should wait seven days after the last daily dose of fluoxetine before beginning the once weekly formulation.

**d.**Initial side effects of fluoxetine are nausea, insomnia, and anxiety. These effects usually resolve

over one to two weeks. Decreased libido, erectile dysfunction, and delayed ejaculation or anorgasmia are common. Addition of bupropion (BuSpar [75 to 150 mg/day in divided doses]) or buspirone (Wellbutrin [10 to 20 mg twice daily]) may alleviate decreased libido, diminished sexual arousal, or impaired orgasm.

**3.Sertraline (Zoloft)** has a low likelihood of interactions with coadministered medications.

**a.**Sertraline is usually started at 50 mg QD; the effective maintenance dose is 50 to 100 mg QD, although doses up to 200 mg QD are necessary in some cases.

**b.**Common initial side effects of sertraline include nausea, diarrhea, insomnia, and sexual dysfunction. It may be more likely than the other SSRIs to cause nausea.

**4.Paroxetine (Paxil)**

**a.**Paroxetine is available generically. Paroxetine substantially inhibits the liver enzyme CYP2D6 and must be used cautiously when coadministered with other drugs metabolized by this enzyme. Paroxetine can cause more anticholinergic side effects than the other SSRIs.

**b.**The usual starting and maintenance dose of paroxetine is 20 mg QD, but can be raised to 40 mg QD if necessary. Paroxetine has a tendency to be mildly sedating. Other side effects include nausea, dry mouth, and sexual dysfunction.

**5.Fluvoxamine (Luvox)**

**a.**Fluvoxamine is a potent inhibitor of the liver enzyme p450 1A2 and has the potential to interact with clozapine and theophylline.

**b.**The usual starting dose of fluvoxamine is 50 mg QD; the therapeutic dose tends to be in the range of 150 to 250 mg. Its side effect profile is similar to the other SSRIs, although it may be more likely to cause nausea.

**6.Escitalopram (Lexapro)** has significantly less p450 interactions than other SSRIs, making it an appealing choice in patients who are on other medications. Escitalopram may cause less sexual dysfunction than other SSRIs. It may have fewer side effects than sertraline. In addition, anxiety symptoms significantly improve. The usual dose is 10 mg qd

**7.Citalopram (Celexa)**

**a.**Citalopram is structurally related to escitalopram.

**b.**The usual starting dose of citalopram is 20 mg QD. The therapeutic dose range tends to be 20 to 40 mg QD in a single morning dose.

**8.Choice of Selective Serotonin Reuptake Inhibitor.** All SSRIs are equally efficacious. Paroxetine may cause more weight gain, discontinuation symptoms and sexual dysfunction than other SSRIs. For patients not taking other drugs that might interact, generic fluoxetine is the best choice. Sertraline and escitalopram cause the fewest drug interactions.

**B.Heterocyclic Antidepressants**. The cyclic antidepressants are less commonly used as first-line antidepressants with the development of the SSRIs and other newer antidepressants. This is mainly due to the less benign side-effect profile of the cyclic antidepressants. In contrast to the SSRIs, the cyclic antidepressants can be fatal in doses as little as five times the therapeutic dose.

**C.Other Antidepressants**

**1.Bupropion (Wellbutrin).** Bupropion is an aminoketone. The rate of seizures caused by bupropion is 0.4 percent, slightly higher than other antidepressants. A slow-release (SR) formulation of bupropion allows for lower peak blood levels and is associated with a seizure incidence of 0.1 percent.

**a.**Because of its mildly stimulating properties, bupropion is often prescribed to depressed patients who have fatigue and poor concentration. It does not have anxiolytic properties.

**b.**The immediate-release form of bupropion is usually started at 100 mg bid and increased to a usual maintenance dose of 200 to 300 mg in 2 or 3 divided doses. The SR allows for twice- or once-daily dosing at 100-150 mg qd-bid.

**c.**The side-effect profile of bupropion is relatively benign. Some patients notice a stimulant-like effect. It is unique among antidepressants in that it does not cause sexual dysfunction. It tends to have a mild appetite-suppressing effect, and may cause mild weight loss.

**2.Venlafaxine (Effexor)** is a phenylethylamine. It is a potent inhibitor of serotonin and norepinephrine reuptake, and a mild inhibitor of dopamine reuptake. It has a benign side-effect profile.

**a.**Dosing for the immediate-release form of venlafaxine typically begins at 37.5 mg bid. If necessary, the medication can be increased by 75 mg every four days to a maximum dose of 375 mg daily in three divided doses.

**b.**For the extended-release form of venlafaxine, dosing frequently begins as a single morning dose of 37.5 mg. The dosage can be increased by 75 mg every four days to a maximum of 225 mg qd in a single daily dose.

**c.**Side effects include nausea, dizziness, insomnia, sedation, and constipation. It can also induce sweating. Venlafaxine may cause blood pressure increases of 3 percent.

**3.Nefazodone (Serzone).** Nefazodone is unique in that it may increase REM sleep. It also may cause less sexual dysfunction than other antidepressants.

**a.**Dosing is usually begun at 100 mg bid. The dose can be increased to 150 mg bid after one week and increased further if necessary to the therapeutic dose range of 300 to 600 mg qd.

**b.**Side effects include dry mouth, constipation, nausea, sedation, and dizziness. Nefazodone increases the blood level of alprazolam and triazolam.

**4.Mirtazapine (Remeron)** is a tetracyclic compound, but is unrelated to TCAs.

**a.**Mirtazapine may possess anxiolytic effects. It can be particularly helpful in depressed patients with insomnia because of sedative properties.

**b.**Dosing is most frequently started at 15 mg qhs, and can be increased to 30 mg or 45 mg qd as needed in one to two week intervals.

**c.**The most notable side effects are sedation, weight gain, and dry mouth. Mirtazapine may have relatively less propensity to cause sexual dysfunction than the SSRIs. Agranulocytosis and neutropenia may rarely occur. Mild transaminase elevations have been noted.

**5.Reboxetine (Vestra)**

**a.**Reboxetine is the first selective norepinephrine reuptake inhibitor (NRI). It may be an appealing treatment option for patients who do not respond to SSRIs. Reboxetine may be more effective than SSRIs in improving social functioning.

**b.**The recommended starting dose is 4 mg BID, with increases after three weeks to 5 mg BID. Reboxetine is fairly well tolerated. The most commonly reported side effects are dry mouth, hypotension, insomnia, decreased sweating, and blurred vision.

**III.Electroconvulsive Therapy (ECT)** is highly effective in patients with delusional depression and with severe melancholic depression on maximum medical therapy. The often quick response and low side-effect profile make ECT one of the most effective ways to address the symptoms of major depression.

**References:** See page 255.

## Generalized Anxiety Disorder

Generalized anxiety disorder (GAD) is characterized by excessive worry and anxiety that are difficult to control and cause significant distress and impairment. Commonly patients develop symptoms of GAD secondary to other DSM-IV diagnoses such as panic disorder, major depression, alcohol abuse, or an axis II personality disorder.

**I.Epidemiology.** GAD is a common anxiety disorder. The prevalence is estimated to be 5 percent in the primary care setting. Twice as many women as men have the disorder. GAD may also be associated with substance abuse, post-traumatic stress disorder, and obsessive compulsive disorder. Between 35 and 50 percent of individuals with major depression meet criteria for GAD.

**II.Clinical manifestations and diagnosis**

**A.The diagnostic criteria for GAD** suggest that patients experience excessive anxiety and worry about a number of events or activities, occurring more days than not for at least six months, that are out of proportion to the likelihood or impact of feared events. Affected patients also present with somatic symptoms, including fatigue, muscle tension, memory loss, and insomnia, and other psychiatric disorders.

**DSM-IV-PC Diagnostic Criteria for Generalized Anxiety Disorder**

1. Excessive anxiety and worry about a number of events or activities, occurring more days than not for at least six months, that are out of proportion to the likelihood or impact of feared events.
2. The worry is pervasive and difficult to control.
3. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms present for more days than not for the past six months):
   Restlessness or feeling keyed up or on edge
   Being easily fatigued
   Difficulty concentrating or mind going blank
   Irritability
   Muscle tension
   Sleep disturbance (difficulty falling or staying asleep, or restless unsatisfying sleep)
4. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

**B.Comorbid psychiatric disorders** and an organic etiology for anxiety must be excluded by careful history taking, a complete physical examination, and appropriate laboratory studies. The medical history should focus upon current medical disorders, medication side effects, or substance abuse to anxiety (or panic) symptoms.

**C.Psychosocial history** should screen for major depression and agoraphobia, stressful life events, family psychiatric history, current social history, substance abuse history (including caffeine, nicotine, and alcohol), and past sexual, physical and emotional abuse, or emotional neglect.
**D.Laboratory studies** include a complete blood count, chemistry panel, serum thyrotropin (TSH) and urinalysis. Urine or serum toxicology measurements or drug levels can be obtained for drugs or medications suspected in the etiology of anxiety.

**Physical Causes of Anxiety-Like Symptoms**

**Cardiovascular**
Angina pectoris, arrhythmias, congestive heart failure, hypertension, hypovolemia, myocardial infarction, syncope (multiple causes), valvular disease, vascular collapse (shock)
**Dietary**
Caffeine, monosodium glutamate (Chinese restaurant syndrome), vitamin-deficiency diseases
**Drug-related**
Akathisia (secondary to antipsychotic drugs), anticholinergic toxicity, digitalis toxicity, hallucinogens, hypotensive agents, stimulants (amphetamines, cocaine, related drugs), withdrawal syndromes (alcohol, sedative-hypnotics), bronchodilators (theophylline, sympathomimetics)
**Hematologic**
Anemias
**Immunologic**
Anaphylaxis, systemic lupus erythematosus
**Metabolic**
Hyperadrenalism (Cushing's disease), hyperkalemia, hyperthermia, hyperthyroidism, hypocalcemia, hypoglycemia, hyponatremia, hypothyroidism, menopause, porphyria (acute intermittent)
**Neurologic**
Encephalopathies (infectious, metabolic, toxic), essential tremor, intracranial mass lesions, postconcussive syndrome, seizure disorders (especially of the temporal lobe), vertigo
**Respiratory**
Asthma, chronic obstructive pulmonary disease, pneumonia, pneumothorax, pulmonary edema, pulmonary embolism
**Secreting tumors**
Carcinoid, insulinoma, pheochromocytoma

**III.Treatment**

**A.Drug therapy.** While benzodiazepines have been the most traditionally used drug treatments for GAD, selective serotonin reuptake inhibitors (SSRIs), selective serotonin and norepinephrine reuptake inhibitors (SNRIs, eg venlafaxine), and buspirone are also effective, and because of their lower side effect profiles and lower risk for tolerance are becoming first-line treatment.

**B.Antidepressants**

**1.Venlafaxine SR (Effexor)** may be a particularly good choice for patients with coexisting psychiatric illness, such as panic disorder, major depression, or social phobia, or when it is not clear if the patient has GAD, depression, or both. Venlafaxine can be started as venlafaxine XR 37.5 mg daily, with dose increases in increments of 37.5 mg every one to two weeks until a dose of 150 mg to 300 mg is attained.

**C.**Tricyclic antidepressants, SSRIs, or SNRIs may be associated with side effects such as restlessness and insomnia. These adverse effects can be minimized by starting at lower doses and gradually titrating to full doses as tolerated.

**1.Selective serotonin reuptake inhibitors**

**a.**Paroxetine (Paxil) 5 to 10 mg qd, increasing to 20 to 40 mg.
**b.**Sertraline (Zoloft) 12.5 to 25 mg qd, increasing to 50 to 200 mg.
**c.**Fluvoxamine (Luvox) 25 mg qd, increasing to 100 to 300 mg.
**d.**Fluoxetine (Prozac) 5 mg qd, increasing to 20 to 40 mg.
**e.**Citalopram (Celexa) 10 mg qd, increasing to 20 to 40 mg.
**f.**Side effects of SSRIs include agitation, headache, gastrointestinal symptoms (diarrhea and nausea), and insomnia. About 20 to 35 percent of patients develop sexual side effects after several weeks or months of SSRI therapy, especially a decreased ability to have an orgasm. Addition of bupropion (75 to 150 mg/day in divided doses) or buspirone (10 to 20 mg twice daily) may alleviate decreased libido, diminished sexual arousal, or impaired orgasm.

**2.Imipramine (Tofranil)**, a starting dose of 10 to 20 mg po at night can be gradually titrated up to 75 to 300 mg each night. Imipramine has anticholinergic and antiadrenergic side effects. Desipramine (Norpramin), 25-200 mg qhs, and nortriptyline (Pamelor), 25 mg tid-qid, can be used as alternatives.

**3.Trazodone (Desyrel)** is a serotonergic agent, but because of its side effects (sedation and priapism), it is not an ideal first-line agent. Daily dosages of 200 to 400 mg are helpful in patients who have not responded to other agents.

**4.Nefazodone (Serzone)** has a similar pharmacologic profile to trazodone, but it is better tolerated and is a good alternative; 100 mg bid; increase to 200-300 mg bid.

**D.Buspirone (BuSpar)** appears to be as effective as the benzodiazepines for the treatment of GAD. However, the onset of action can be several weeks, and there are occasional gastrointestinal side effects. Advantages of using buspirone instead of benzodiazepines include the lack of abuse potential, physical dependence, or withdrawal, and lack of potentiation of alcohol or other sedative-hypnotics. Most patients need to be titrated to doses of 30 to 60 mg per day given in two or three divided doses.

**E.Benzodiazepines.** Several controlled studies have demonstrated the efficacy of benzodiazepines (eg, chlordiazepoxide, diazepam, alprazolam) in the treatment of GAD.

**1.**Many anxious patients who start on benzodiazepines have difficulty stopping them, particularly since rebound anxiety and withdrawal symptoms can be moderate to severe. Methods of facilitating withdrawal and decreasing rebound symptoms include tapering the medication slowly, converting short-acting benzodiazepines to a long-acting preparation (eg, clonazepam) prior to tapering, and treating the patient with an antidepressant before attempting to taper.

**2.**Symptoms of anxiety can be alleviated in most cases of GAD with clonazepam (Klonopin) 0.25 to 0.5 mg po bid titrated up to 1 mg bid or tid, or lorazepam (Ativan) 0.5 to 1.0 mg po tid titrated up to 1 mg po tid or qid. Often an antidepressant is prescribed concomitantly. After six to eight weeks, when the antidepressant begins to have its optimal effects, the benzodiazepine usually should be tapered over months, achieving roughly a 10 percent dose reduction per week.

**Benzodiazepines Commonly Prescribed for Anxiety Disorders**

| Name | Half-life (hours) | Dosage range (per day) | Initial dosage |
|---|---|---|---|
| Alprazolam (Xanax) | 14 | 1 to 4 mg | 0.25 to 0.5 mg four times daily |
| Chlordiazepoxide (Librium) | 20 | 15 to 40 mg | 5 to 10 mg three times daily |
| Clonazepam (Klonopin) | 50 | 0.5 to 4.0 mg | 0.5 to 1.0 mg twice daily |
| Clorazepate (Tranxene) | 60 | 15 to 60 mg | 7.5 to 15.0 mg twice daily |
| Diazepam (Valium) | 40 | 6 to 40 mg | 2 to 5 mg three times daily |
| Lorazepam (Ativan) | 14 | 1 to 6 mg | 0.5 to 1.0 mg three times daily |
| Oxazepam (Serax) | 9 | 30 to 90 mg | 15 to 30 mg three times daily |

**F.**Agents with short half-lives, such as oxazepam (Serax), do not cause excessive sedation. These agents should be used in the elderly and in patients with liver disease. They are also suitable for use on an "as-needed" basis. Agents with long half-lives, such as clonazepam (Klonopin), should be used in younger patients who do not have concomitant medical problems. The longer-acting agents can be taken less frequently during the day, patients are less likely to experience anxiety between doses and withdrawal symptoms are less severe.

**References:** See page 255.

## Panic Disorder

Panic disorder is characterized by the occurrence of panic attacks--sudden, unexpected periods of intense fear or discomfort. About 15% of the general population experiences panic attacks; 1.6-3.2% of women and 0.4%-1.7% of men have panic disorder.

**DSM-IV Criteria for panic attack**

A discrete period of intense fear or discomfort in which four or more of the following symptoms developed abruptly and reached a peak within 10 minutes.

- Chest pain or discomfort
- Choking
- Depersonalization or derealization
- Dizziness, faintness, or unsteadiness
- Fear of "going crazy" or being out of control
- Fear of dying
- Flushes or chills
- Nausea or gastrointestinal distress
- Palpitations or tachycardia
- Paresthesias
- Shortness of breath (or feelings of smothering)
- Sweating
- Trembling or shaking

**Diagnostic criteria for panic disorder without agoraphobia**

Recurrent, unexpected panic attacks

**And**

At least one attack has been followed by at least 1 month of one (or more) of the following:

Persistent concern about experiencing more attacks

Worry about the meaning of the attack or its consequences (fear of losing control, having a heart attack, or "going crazy")

A significant behavioral change related to the attacks

**And**

Absence of agoraphobia

**And**

Direct physiological effects of a substance (drug abuse or medication) or general medical condition has been ruled out as a cause of the attacks

**And**

The panic attacks cannot be better accounted for by another mental disorder

## I. Clinical evaluation

**A.** Panic attacks are manifested by the sudden onset of an overwhelming fear, accompanied by feelings of impending doom, for no apparent reason.

**B.** The essential criterion for panic attack is the presence of 4 of 13 cardiac, neurologic, gastrointestinal, or respiratory symptoms that develop abruptly and reach a peak within 10 minutes. The physical symptoms include shortness of breath, dizziness or faintness, palpitations, accelerated heart rate, and sweating. Trembling, choking, nausea, numbness, flushes, chills, or chest discomfort are also common, as are cognitive symptoms such as fear of dying or losing control.

**C.** One third of patients develop agoraphobia, or a fear of places where escape may be difficult, such as bridges, trains, buses, or crowded areas. Medications, substance abuse, and general medical conditions such as hyperthyroidism must be ruled out as a cause of the patient's symptoms.

**D.** The history should include details of the panic attack, its onset and course, history of panic, and any treatment. Questioning about a family history of panic disorder, agoraphobia, hypochondriasis, or depression is important. Because panic disorder may be triggered by marijuana or stimulants such as cocaine, a history of substance abuse must be identified. A medication history, including prescription, over-the-counter, and herbal preparations, is essential.

**E.** The patient should be asked about stressful life events or problems in daily life that may have preceded onset of the disorder. The extent of any avoidance behavior that has developed or suicidal ideation, self-medication, or exacerbation of an existing medical disorder should be assessed.

## II. Management

**A.** Patients should reduce or eliminate caffeine consumption, including coffee and tea, cold medications, analgesics, and beverages with added caffeine. Alcohol use is a particularly insidious problem because patients may use drinking to alleviate the panic.

| Pharmacologic treatment of panic disorder | | |
|---|---|---|
| | Dosage range (mg/d) | |
| **Drug** | **Initial** | **Therapeutic** |
| **SSRIs** | | |
| Fluoxetine (Prozac) | 5-10 | 10-60 |
| Fluvoxamine (LuVox) | 25-50 | 25-300 |
| Paroxetine (Paxil) | 10-20 | 20-50 |
| Sertraline (Zoloft) | 25-50 | 50-200 |
| Citalopram (Celexa) | 10-20 mg qd | 20-40 |
| **Benzodiazepines** | | |
| Alprazolam (Xanax) | 0.5 In divided doses, tid-qid | 1-4 In divided doses, tid-qid |
| Alprazolam XR (Xanax XR) | 0.5 to 1 mg/day given once in the morning. | 3-6 mg qAM |
| Clonazepam (Klonopin) | 0.5 In divided doses, bid-tid | 1-4 In divided doses, bid-tid |
| Diazepam (Valium) | 2.0 In divided doses, bid-tid | 2-20 In divided doses, bid |
| Lorazepam (Ativan) | 0.5 In divided doses, bid-tid | 1-4 In divided doses, bid-tid |
| **TCAs** | | |
| Amitriptyline (Elavil) | 10 | 10-300 |
| Clomipramine (Anafranil) | 25 | 25-300 |
| Desipramine (Norpramin) | 10 | 10-300 |
| Imipramine (Tofranil) | 10 | 10-300 |
| Nortriptyline (Pamelor) | 10 | 10-300 |
| **MAOIs** | | |
| Phenelzine (Nardil) | 15 | 15-90 |
| Tranylcypromine (Parnate) | 10 | 10-30 |

**B.Selective serotonin reuptake inhibitors (SSRIs)** are an effective, well-tolerated alternative to benzodiazepines and TCAs. SSRIs are superior to either imipramine or alprazolam. They lack the cardiac toxicity and anticholinergic effects of TCAs. Fluoxetine (Prozac), fluvoxamine (LuVox), paroxetine (Paxil), sertraline (Zoloft), and citalopram (Celexa) have shown efficacy for the treatment of panic disorder.

**C.Tricyclic antidepressants (TCAs)** have demonstrated efficacy in treating panic. They are, however, associated with a delayed onset of action and side effects--particularly orthostatic hypotension, anticholinergic effects, weight gain, and cardiac toxicity.

**D.Benzodiazepines**

**1.**Clonazepam (Klonopin), alprazolam (Xanax), and lorazepam (Ativan), are effective in blocking panic attacks. Advantages include a rapid onset of therapeutic effect and a safe, favorable, side-effect profile. Among the drawbacks are the potential for abuse and dependency, worsening of depressive symptoms, withdrawal symptoms on abrupt discontinuation, anterograde amnesia, early relapse on discontinuation, and inter-dose rebound anxiety.

**2.**Benzodiazepines are an appropriate first-line treatment only when rapid symptom relief is needed. The most common use for benzodiazepines is to stabilize severe initial symptoms until another treatment (eg, an SSRI or cognitive behavioral therapy) becomes effective.

**3.**The starting dose of alprazolam is 0.5 mg bid. Approximately 70% of patients will experience a discontinuance reaction characterized by increased anxiety, agitation, and insomnia when alprazolam is tapered. Clonazepam's long duration of effect diminishes the need for multiple daily dosing. Initial symptoms of sedation and ataxia are usually transient.

**E.Monoamine oxidase inhibitors (MAOIs).** MAOIs such phenelzine sulfate (Nardil) may be the most effective agents for blocking panic attacks and for relieving the depression and concomitant social anxiety of panic disorder. Recommended doses range from 45-90 mg/d. MAOI use is limited by adverse effects such as orthostatic hypotension, weight gain, insomnia, risk of hypertensive crisis, and the need for dietary monitoring. MAOIs are often reserved for patients who do not respond to safer drugs.

**F.Beta-blockers** are useful in moderating heart rate and decreasing dry mouth and tremor; they are less effective in relieving subjective anxiety.

**References:** See page 255.

# Insomnia

Insomnia is the perception by patients that their sleep is inadequate or abnormal. Insomnia may affect as many as 69% of adult primary care patients. The incidence of sleep problems increases with age. Younger persons are apt to have trouble falling asleep, whereas older persons tend to have prolonged awakenings during the night.

**I.Causes of insomnia**

**A.Situational stress** concerning job loss or problems often disrupt sleep. Patients under stress may experience interference with sleep onset and early morning awakening. Attempting to sleep in a new place, changes in time zones, or changing bedtimes due to shift work may interfere with sleep.

**B.Drugs associated with insomnia** include antihypertensives, caffeine, diuretics, oral contraceptives, phenytoin, selective serotonin reuptake inhibitors, protriptyline, corticosteroids, stimulants, theophylline, and thyroid hormone.

**C.Psychiatric disorders.** Depression is a common cause of poor sleep, often characterized by early morning awakening. Associated findings include hopelessness, sadness, loss of appetite, and reduced enjoyment of formerly pleasurable activities. Anxiety disorders and substance abuse may cause insomnia.

**D.Medical disorders.** Prostatism, peptic ulcer, congestive heart failure, and chronic obstructive pulmonary disease may cause insomnia. Pain, nausea, dyspnea, cough, and gastroesophageal reflux may interfere with sleep.

**E.Obstructive sleep apnea syndrome**

**1.**This sleep disorder occurs in 5-15% of adults. It is characterized by recurrent discontinuation of breathing during sleep for at least 10 seconds. Abnormal oxygen saturation and sleep patterns result in excessive daytime fatigue and drowsiness. Loud snoring is typical. Overweight, middle-aged men are particularly predisposed. Weight loss can be helpful in obese patients.

**2.**Diagnosis is by polysomnography. Use of hypnotic agents is contraindicated since they increase the frequency and the severity of apneic episodes.

**II.Clinical evaluation of insomnia**

**A.**Acute personal and medical problems should be sought, and the duration and pattern of symptoms and use of any psychoactive agents should be investigated. Substance abuse, leg movements, sleep apnea, loud snoring, nocturia, and daytime napping or fatigue should be sought.

**B.**Consumption of caffeinated beverages, prescribed drugs, over-the-counter medications, and illegal substances should be sought.

**III.Pharmacologic management**

**A.**Hypnotics are the primary drugs used in the management of insomnia. These drugs include the benzodiazepines and the benzodiazepine receptor agonists in the imidazopyridine or pyrazolopyrimidine classes.

**Recommended dosages of hypnotic medications (elderly dosages are in parentheses)**

| Benzodiazepine hypnotics | Recommended dose, mg | $T_{max}$ | Elimination half-life | Receptor selectivity |
|---|---|---|---|---|
| **Benzodiazepine receptor agonists** | | | | |
| Zolpidem (Ambien) | 5-10 (5) | 1.6 | 2.6 | Yes |
| Zaleplon (Sonata) | 5-10 (5) | 1 | 1 | Yes |
| **Hypnotic Medications** | | | | |
| Estazolam (ProSom) | 1-2 (0.5-1) | 2.7 | 17.1 | No |
| Flurazepam (Dalmane) | 15-30 (15) | 1 | 47.0-100 | No |
| Triazolam (Halcion) | 0.250 (0.125) | 1.2 | 2.6 | No |
| Temazepam (Restoril) | 7.5-60 (7.5-20) | 0.8 | 8.4 | No |
| Quazepam (Doral) | 7.5-15.0 (7.5) | 2 | 73 | No |

**B.**Zolpidem (Ambien) and zaleplon (Sonata) have the advantage of achieving hypnotic effects with less tolerance and fewer adverse effects.

**C.**The safety profile of these benzodiazepines and benzodiazepine receptor agonists is good; lethal

overdose is rare, except when benzodiazepines are taken with alcohol. Sedative effects may be enhanced when benzodiazepines are used in conjunction with other central nervous system depressants.

**D.Zolpidem (Ambien)** is a benzodiazepine agonist with a short elimination half-life that is effective in inducing sleep onset and promoting sleep maintenance. Zolpidem may be associated with greater residual impairment in memory and psychomotor performance than zaleplon.

**E.Zaleplon (Sonata)** is a benzodiazepine receptor agonist that is rapidly absorbed ($T_{MAX}$ = 1 hour) and has a short elimination half-life of 1 hour. Zaleplon does not impair memory or psychomotor functioning at as early as 2 hours after administration, or on morning awakening. Zaleplon does not cause residual impairment when the drug is given in the middle of the night. Zaleplon can be used at bedtime or after the patient has tried to fall asleep naturally.

**F.Benzodiazepines with long half-lives**, such as flurazepam (Dalmane), may be effective in promoting sleep onset and sustaining sleep. These drugs may have effects that extend beyond the desired sleep period, however, resulting in daytime sedation or functional impairment. Patients with daytime anxiety may benefit from the residual anxiolytic effect of a long-acting benzodiazepine administered at bedtime. Benzodiazepines with intermediate half-lives, such as temazepam (Restoril), facilitate sleep onset and maintenance with less risk of daytime residual effects.

**G.Benzodiazepines with short half-lives**, such as triazolam (Halcion), are effective in promoting the initiation of sleep but may not contribute to sleep maintenance.

**H.Sedating antidepressants** are sometimes used as an alternative to benzodiazepines or benzodiazepine receptor agonists. Amitriptyline (Elavil), 25-50 mg at bedtime, or trazodone (Desyrel), 50-100 mg, are common choices.

**References:** See page 255.

## Nicotine Dependence

Smoking causes approximately 430,000 smoking deaths each year, accounting for 19.5% of all deaths. Daily use of nicotine for several weeks results in physical dependence. Abrupt discontinuation of smoking leads to nicotine withdrawal within 24 hours. The symptoms include craving for nicotine, irritability, frustration, anger, anxiety, restlessness, difficulty in concentrating, and mood swings. Symptoms usually last about 4 weeks.

**I.Drugs for treatment of nicotine dependance**

**A.**Treatment with nicotine is the only method that produces significant withdrawal rates. Nicotine replacement comes in three forms: nicotine polacrilex gum (Nicorette), nicotine transdermal patches (Habitrol, Nicoderm, Nicotrol), and nicotine nasal spray (Nicotrol NS) and inhaler (Nicotrol). Nicotine patches provide steady-state nicotine levels, but do not provide a bolus of nicotine on demand as do sprays and gum.

**B.Bupropion (Zyban)** is an antidepressant shown to be effective in treating the craving for nicotine. The symptoms of nicotine craving and withdrawal are reduced with the use of bupropion, making it a useful adjunct to nicotine replacement systems.

**Treatments for nicotine dependence**

| Drug | Dosage | Comments |
|---|---|---|
| Nicotine gum (Nicorette) | 2- or 4-mg piece/30 min | Available OTC; poor compliance |
| Nicotine patch (Habitrol, Nicoderm CQ) | 1 patch/d for 6-12 wk, then taper for 4 wk | Available OTC; local skin reactions |
| Nicotine nasal spray (Nicotrol NS) | 1-2 doses/h for 6-8 wk | Rapid nicotine delivery; nasal irritation initially |
| Nicotine inhaler (Nicotrol Inhaler) | 6-16 cartridges/d for 12 wk | Mimics smoking behavior; provides low doses of nicotine |
| Bupropion (Zyban) | 150 mg/day for 3 d, then titrate to 300 mg | Treatment initiated 1 wk before quit day; contraindicated with seizures, anorexia, heavy alcohol use |

**C.Nicotine polacrilex (Nicorette)** is available OTC. The patient should use 1-2 pieces per hour. A 2-mg dose is recommended for those who smoke fewer than 25 cigarettes per day, and 4 mg for heavier smokers. It is used for 6 weeks, followed by 6 weeks of tapering. Nicotine gum improves smoking cessation rates by about 40%-60%. Drawbacks include poor compliance and unpleasant taste.

**D.Transdermal nicotine (Habitrol, Nicoderm, Nicotrol)** doubles abstinence rates compared with placebo, The patch is available OTC and is easier to use than the gum. It provides a plateau level of nicotine at about half that of what a pack-a-day smoker would normally obtain. The higher dose should be used for 6-12 weeks followed by 4 weeks of tapering.

**E.Nicotine nasal spray (Nicotrol NS)** is available by prescription and is a good choice for patients who have not been able to quit with the gum or patch or for heavy smokers. It delivers a high level of nicotine, similar to smoking. Nicotine nasal spray doubles the rates of sustained abstinence. The spray is used 6-8 weeks, at 1-2 doses per hour (one puff in each nostril). Tapering over about 6 weeks. Side effects include nasal and throat irritation, headache, and eye watering.

**F.Nicotine inhaler (Nicotrol Inhaler)** delivers nicotine orally via inhalation from a plastic tube. It is available by prescription and has a success rate of 28%, similar to nicotine gum. The inhaler has the advantage of avoiding some of the adverse effects of nicotine gum, and its mode of delivery more closely resembles the act of smoking.

**G.Bupropion (Zyban)**

**1.**Bupropion is appropriate for patients who have been unsuccessful using nicotine replacement. Bupropion reduces withdrawal symptoms and can be used in conjunction with nicotine replacement therapy. The treatment is associated with reduced weight gain. Bupropion is contraindicated with a history of seizures, anorexia, heavy alcohol use, or head trauma.

**2.**Bupropion is started at a dose of 150 mg daily for 3 days and then increased to 300 mg daily for 2 weeks before the patient stops smoking. Bupropion is then continued for 3 months. When a nicotine patch is added to this regimen, the abstinence rates increase to 50% compared with 32% when only the patch is used.

**References:** See page 255.

## Anorexia Nervosa

Anorexia nervosa is a psychologic illness characterized by marked weight loss, an intense fear of gaining weight even though the patient is underweight, a distorted body image and amenorrhea. Anorexia primarily affects adolescent girls and occurs in approximately 0.2 to 1.3 percent of the general population.

### I.Diagnosis and Clinical Features

**A.**The typical patient with anorexia nervosa is an adolescent female who is a high achiever. She usually has successful parents and feels compelled to excel. She is a perfectionist and a good student, involved in many school and community activities.

**DSM-IV Diagnostic Criteria for Anorexia Nervosa**

- Refusal to maintain body weight at or above a minimally normal weight for age and height (eg, weight loss leading to maintenance of body weight less than 85 percent of that expected; or failure to make expected weight gain during a period of growth, leading to body weight less than 85 percent of that expected).
- Intense fear of gaining weight or becoming fat, even though underweight.
- Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight.
- In postmenarchal females, amenorrhea, ie, the absence of at least three consecutive menstrual cycles. (A woman is considered to have amenorrhea if her periods occur only following hormone, eg, estrogen, administration.)

**Specify type:**

- Restricting type: During the current episode of anorexia nervosa, the person has not regularly engaged in binge-eating or purging behavior (ie, self-induced vomiting or the misuse of laxatives, diuretics or enemas).
- Binge-eating/purging type: During the current episode of anorexia nervosa, the person has regularly engaged in binge-eating or purging behavior (ie, self-induced vomiting or the misuse of laxatives, diuretics or enemas).

**B.**Persons with anorexia nervosa have a disturbed perception of their own weight and body shape. Individuals

perceive themselves as overweight even though they are emaciated.

| Features Associated with Anorexia Nervosa | |
|---|---|
| Bulimic episodes<br>Preparation of elaborate meals for others but self-limitation to a narrow selection of low-calorie foods Obsessive-compulsive, behaviors<br>Denial or minimization of illness<br>Delayed psychosexual development<br>Hypothermia<br>Bradycardia<br>Hypotension | Edema<br>Lanugo<br>Overactivity, exercise<br>Early satiety<br>Constipation<br>Skin dryness<br>Hypercarotenemia<br>Hair loss<br>Dehydration |

**II.Treatment**

**A.**A trial of outpatient treatment may be attempted if the patient is not severely emaciated, has had the illness for less than six months, has no serious medical complications, is accepting her illness and is motivated to change, and has supportive and cooperative family and friends.

**B.**The first step in the treatment of anorexia nervosa is correction of the starvation state. A goal weight should be set and the patient's weight should be monitored once or twice a week in the office. A caloric intake to provide a weight gain of 1 to 3 lb per week should be instituted. Initially, weight gain should be gradual to prevent gastric dilation, pedal edema and congestive heart failure. Often, a nutritional supplement is added to the regimen to augment dietary intake.

**C.**During the process of refeeding, weight gain as well as electrolyte levels should be strictly monitored. The disturbed eating behavior must be addressed in specific counseling sessions.

**D.**Inpatient treatment is indicated if weight loss exceeds 30 percent of ideal weight; patient is having suicidal thoughts; patient is abusing laxatives, diuretics or diet pills, or outpatient treatment has failed.

**E.**The drug of choice for the treatment of anorexia nervosa is food. In cases of depression refractory to proper nutrition, an antidepressant may be helpful. The use of serotonin-specific reuptake inhibitors (SSRIs) is common and has proved to alleviate the depressed mood and moderate obsessive-compulsive behaviors. Fluoxetine (Prozac) has been used successfully in the therapy of anorexia and bulimia; 20-40 mg PO qAM.

**References:** See page 255.

## Bulimia Nervosa

Bulimia nervosa is characterized by binge eating and inappropriate vomiting, fasting, excessive exercise and the misuse of diuretics, laxatives or enemas. Bulimia nervosa is 10 times more common in females than in males and affects up to 3 percent of young women. The condition usually becomes symptomatic between the ages of 13 and 20 years.

**I.Diagnostic criteria**

**A.**The diagnostic criteria for bulimia nervosa now include subtypes to distinguish patients who compensate for binge eating by purging (vomiting and/or the abuse of laxatives and diuretics) from those who use nonpurging behaviors (eg, fasting or excessive exercising).

**II.Patient evaluation**

**A.**Physical examination should include vital signs and an evaluation of height and weight relative to age. Hair loss, lanugo, abdominal tenderness, acrocyanosis (cyanosis of the extremities), jaundice, edema, parotid gland tenderness or enlargement, and scars on the dorsum of the hand should be sought.

**B.Laboratory tests** include a complete blood count with differential, serum chemistry and thyroid profiles, and urine chemistry microscopy testing. A chest radiograph and electrocardiogram may be indicated in some cases.

**C.Psychiatric assessment**

**1.**Standardized testing should document the patient's general personality features, characterologic disturbance and attitudes about eating, body size and weight.

**2.**A complete history should document the patient's body weight, eating patterns and attempts at weight loss, including typical daily food intake, methods of purging and perceived ideal weight.

**3.**The patient's interpersonal history and functioning, including family dynamics, peer relationships, and present or past physical, sexual or emotional abuse should be assessed. An evaluation of medical and psychiatric comorbidity, as well as documentation of previous attempts at treatment.

**DSM IV Diagnostic Criteria for Bulimia Nervosa**

- Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following:
- Eating, in a discrete period of time (eg, within a two-hour period), an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances.
- A sense of lack of control over eating during the episode (eg, a feeling that one cannot stop eating or control what or how much one is eating).
- Recurrent inappropriate compensatory behavior in order to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, enemas, or other medications; fasting or excessive exercise.
- The binge eating and inappropriate compensatory behaviors both occur, on average, at least twice a week for three months.
- Self-evaluation is unduly influenced by body shape and weight.
- The disturbance does not occur exclusively during episodes of anorexia nervosa.

***Specify type:***

- **Purging type:** during the current episode of bulimia nervosa, the person has regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics, or enemas.
- **Nonpurging type:** during the current episode of bulimia nervosa, the person has used other inappropriate compensatory behaviors, such as fasting or excessive exercise, but has not regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics, or enemas.

**III.Treatment**

**A.Tricyclic antidepressants.** Desipramine, 150 to 300 mg per day, is superior to placebo in the treatment of bulimia nervosa. Imipramine, 176 to 300 mg per day, is also beneficial. Amitriptyline, 150 mg per day, is effective in reducing binge eating (72 percent).

**B.Selective serotonin reuptake inhibitors.** Fluoxetine (Prozac), 20-mg dosage, results in a 45 percent reduction in binge eating. Fluoxetine in a dosage of 60 mg per day produces the best treatment response, demonstrating a 67 percent reduction in binge eating.

**C.Psychotherapy**. Cognitive-behavioral therapy has resulted in the most significant reductions of binge eating and/or purging. Cognitive-behavioral therapy principally involves interventions aimed at addressing preoccupation with body, weight and food, perfectionism, dichotomous thinking and low self-esteem. The initial goal of cognitive-behavioral therapy is to restore control over dietary intake.

**References:** See page 255.

## Alcohol and Drug Addiction

The prevalence of alcohol disorders is 16-28%, and the prevalence of drug disorders is 7-9%. Alcoholism is characterized by impaired control over drinking, preoccupation with alcohol, use of alcohol despite adverse consequences, and distortions in thinking (denial). Substance abuse is a pattern of misuse during which the patient maintains control. Addiction or substance dependence is a pattern of misuse during which the patient has lost control.

**I.Clinical assessment of alcohol use and abuse**

**A.**The amount and frequency of alcohol use and other drug use in the past month, week, and day should be determined. Whether the patient ever consumes five or more drinks at a time (binge drinking) and previous abuse of alcohol or other drugs should be assessed.

**B.**Effects of the alcohol or drug use on the patient's life may include problems with health, family, job or financial status or with the legal system. History of blackouts, motor vehicle crashes, and the effect of alcohol use on family members or friends should be evaluated.

**Clinical Clues to Alcohol and Drug Disorders**

| | |
|---|---|
| **Social history** | |
| Arrest for driving under the influence | Family instability (divorce, separation) |
| Loss of job or sent home from work for alcohol- or drug-related reasons | Frequent, unplanned absences |
| Domestic violence | Personal isolation |
| Child abuse/neglect | Problems at work/school |
| | Mood swings |

| | |
|---|---|
| **Medical history**<br>History of addiction to any drug<br>Withdrawal syndrome<br>Depression<br>Anxiety disorder<br>Recurrent pancreatitis<br>Recurrent hepatitis<br>Hepatomegaly<br>Peripheral neuropathy<br>Myocardial infarction at less than age 30 (cocaine)<br>Blood alcohol level greater than 300 mg per dL or greater than 100 mg per dL | Alcohol smell on breath or intoxicated during office visit<br>Tremor<br>Mild hypertension<br>Estrogen-mediated signs (telangiectasias, spider angiomas, palmar erythema, muscle atrophy)<br>Gastrointestinal complaints<br>Sleep disturbances<br>Eating disorders<br>Sexual dysfunction |

**DSM-IV Diagnostic Criteria for Substance Dependence**

A maladaptive pattern of substance use leading to clinically significant impairment or distress as manifested by 3 or more of the following occurring at any time during the same 12-month period.

**Tolerance, as defined by one of the following:**

- A need for markedly increased amounts of the substance to achieve intoxication of the desired effect.
- Markedly diminished effect with continued use of the same amount of the substance.

**Withdrawal, as manifested by one of the following:**

- The characteristic withdrawal syndrome for the substance.
- The same, or a closely related, substance is taken to relieve or avoid withdrawal symptoms.
- The substance is often taken in larger amounts or over a longer period than was intended.
- There is a persistent desire or unsuccessful efforts to cut down or control substance use.
- A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects.
- Important social, occupational, or recreational activities are given up or reduced because of substance use.
- Substance use is continued despite knowledge of having a persistent or recurrent physical or psychologic problem that is likely caused or exacerbated by the substance.

**II.Laboratory screening**

**A.Mean corpuscular volume.** An elevated mean corpuscular volume (MCV) level may result from folic acid deficiency, advanced alcoholic liver disease, or the toxic effect of alcohol on red blood cells. MCV has poor sensitivity for predicting addiction.

**B.Gamma-glutamyltransferase.** The sensitivity of GGT for predicting alcohol addiction is higher than that of MCV, but its specificity is low.

**C.Other liver function test** results may be elevated because of heavy alcohol consumption, including aspartate aminotransferase (AST) and alanine aminotransferase (ALT). These markers have low sensitivity and specificity. An AST/ALT ratio greater than 2:1 is highly suggestive of alcohol-related liver disease.

**D.Carbohydrate-deficient transferrin (CDT).** Consumption of 4 to 7 drinks daily for at least 1 week results in a decrease in the carbohydrate content of transferrin. The sensitivity and specificity of CDT are high.

**III.Alcohol intoxication.** Support is the main treatment for alcohol intoxication. Respiratory depression is frequently the most serious outcome. Unconscious patients should receive thiamine intravenously before receiving glucose.

**IV.Alcohol withdrawal**. Treatment consists of four doses of chlordiazepoxide (Librium), 50 mg every 6 hours, followed by 3 doses of 50 mg every 8 hours, followed by 2 doses of 50 mg every 12 hours, and finally 1 dose of 50 mg at bedtime.

| Signs and Symptoms of Alcohol Withdrawal |
|---|
| Withdrawal is characterized by the development of a combination of any of the following signs and symptoms several hours after stopping a prolonged period of heavy drinking: |
| 1. Autonomic hyperactivity: diaphoresis, tachycardia, elevated blood pressure<br>2. Tremor<br>3. Insomnia<br>4. Nausea or vomiting<br>5. Transient visual, tactile, or auditory hallucinations or illusions<br>6. Psychomotor agitation<br>7. Anxiety<br>8. Generalized seizure activity |

**Management of Alcohol Withdrawal**

| Clinical Disorder | Mild/Moderate AWS, able to take oral | Mild/Moderate AWS, unable to take oral | Severe AWS |
|---|---|---|---|
| Adrenergic Hyperactivity | Lorazepam (Ativan) 2 mg po q2h or Chlordiazepoxide (Librium) 25-100 mg po q6h | Lorazepam 1-2 mg IM/IV q1-2h as needed | Lorazepam 1-2 mg IV q 5-10 min |
| Dehydration | Water or juice po | NS 1 liter bolus, then D5NS 150-200 mL/h | Aggressive hydration with NS /D5NS |
| Nutritional Deficiency | Thiamine 100 mg po<br>Multivitamins<br>Folate 1 mg po | Thiamine 100 mg IV<br>Multivitamins 1 amp in first liter of IV fluids<br>Folate 1 mg IV in first liter of IV fluids | Thiamine 100 mg IV<br>Multivitamins 1 amp in first liter of IV fluids<br>Folate 1 mg IV in first liter of IV fluids |
| Hypoglycemia | High fructose solution po | 25 mL D50 IV (repeat as necessary) | 25 mL D50 IV (repeat as necessary) |
| Hyperthermia | | | Cooling blankets |
| Seizures | Lorazepam (Ativan) 2 mg IV | Lorazepam 2 mg IV | Lorazepam 2 mg IV |

**V.Sedative-hypnotic withdrawal**. Establishment of physical dependence usually requires daily use of therapeutic doses of these drugs for 6 months or higher doses for 3 months. Treatment of withdrawal from sedative-hypnotics is similar to that of withdrawal from alcohol; chlordiazepoxide (Librium) and lorazepam (Ativan) are the drugs of choice.

**VI.Maintenance treatment**

**A.Twelve-step programs** make a significant contribution to recovery. Alcoholics Anonymous (AA) is the root of 12-step programs.

**B.Drugs for treatment of alcohol addiction**

**1.Disulfiram** inhibits aldehyde dehydrogenase. On ingesting alcohol, patients taking disulfiram experience flushing of the skin, palpitations, decreased blood pressure, nausea, vomiting, shortness of breath, blurred vision, and confusion. Death has been reported. Side effects include drowsiness, lethargy, peripheral neuropathy, hepatotoxicity, and hypertension. The usual dose is 250 to 500 mg daily.

**2.Naltrexone,** an opioid antagonist, reduces drinking. It has diminished effectiveness over time and does not reduce relapse rates.

**3.Serotonergic drugs** reduce drinking in heavy-drinking, nondepressed alcoholic patients, but only 15% to 20% from pretreatment levels.

**4.Acamprosate (calcium acetylhomotaurinate)** reduces the craving for alcohol. Acamprosate appears to result in more frequent and longer-lasting periods of abstinence than does naltrexone.

## VII.Opiates

### Signs and Symptoms of Opiate Withdrawal

1. Mild elevation of pulse and respiratory rates, blood pressure, and temperature
2. Piloerection (gooseflesh)
3. Dysphoric mood and drug craving
4. Lacrimation and/or rhinorrhea
5. Mydriasis, yawning, and diaphoresis
6. Anorexia, abdominal cramps, vomiting, and diarrhea
7. Insomnia
8. Weakness

### Agents Used to Treat Opiate Withdrawal

**Methadone (Dolophine)** is a pure opioid agonist restricted to inpatient treatment or specialized outpatient drug treatment programs. Treatment is a 15- to 20-mg daily dose for 2 to 3 days, followed by a 10 to 15 percent reduction in daily dose.

**Clonidine (Catapres)** is an alpha-adrenergic blocker. One 0.2-mg dose every 4 hours to relieve symptoms of withdrawal may be effective. It may be continued for 10 to 14 days, followed by tapering.

**Buprenorphine (Buprenex)** is a partial mu-receptor agonist which can be administered sublingually in doses of 2, 4, or 8 mg every 4 hours for the management of opiate withdrawal symptoms.

**Naltrexone (ReVia, Trexan)/clonidine** involves pretreatment with 0.2 to 0.3 mg of clonidine, followed by 12.5 mg of naltrexone (a pure opioid antagonist). Naltrexone is increased to 25 mg on day 2, 50 mg on day 3, and 100 mg on day 4, with clonidine doses of 0.1 to 0.3 mg 3 times daily.

## VIII.Stimulant Drugs

### Signs and Symptoms of Cocaine or Stimulant Withdrawal

1. Dysphoric mood
2. Fatigue, malaise
3. Vivid, unpleasant dreams
4. Sleep disturbance
5. Increased appetite
6. Psychomotor retardation or agitation

**A.**Stimulant withdrawal is treated with bromocriptine (Parlodel). This drug reduces stimulant craving and withdrawal symptoms. Bromocriptine dosage is 0.625 to 2.5 mg taken orally three times daily.
**B.**An alternative protocol uses desipramine to reduce the stimulant craving and postwithdrawal symptoms. Desipramine may be used alone or with bromocriptine. The initial dosage of desipramine is 50 mg per day taken orally. This dosage is increased until a dosage of 150 to 200 mg is achieved. Paranoia or combativeness is treated with lorazepam, 2-mg IM.

## References

References may be obtained at www.ccspublishing.com.