The Bellevue Guide to Outpatient Medicine

An evidence-based guide to primary care

edited by
Nate Link, Michael Tanner, Danielle Ofri and Lloyd Wasserman

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The Bellevue Guide to Outpatient Medicine

An evidence-based guide to primary care

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Introduction

The Bellevue Guide to Outpatient Medicine represents a collaboration among primary care and specialist attending physicians in the Department of Medicine at New York University School of Medicine. It is intended for use by teachers and practitioners of primary care in their daily work. In the spirit of evidence-based practice, the guide presents data about prevalence of disease, accuracy of diagnostic tests, and measures of treatment efficacy. Readers are encouraged to use these data to tailor clinical decisions for their individual patients. While clinical guidelines have successfully promoted improved standards of care, we believe the ultimate expression of evidence-based medicine incorporates these primary data into daily medical decision-making on a case by case basis. It is hoped that clinicians will find the guide to be a useful aid for patient-centered decision making as well as a source of intellectual nourishment.

The Bellevue Guide began in 1995 as an initiative to improve patient care at Bellevue Hospital Center. Previous iterations have been used extensively by attending physicians and house staff at Bellevue and other area hospitals. The current edition is updated and expanded to include most of the commonly encountered outpatient problems in primary care. Although all editors and authors of the guide are current or former clinicians of Bellevue Hospital and its sister facility, Gouverneur Diagnostic and Treatment Center, the guide does not represent official views or policies of these institutions.

The Bellevue Guide is dedicated to Bellevue’s patients whose health and well being represent the primary mission of the guide and its authors. We acknowledge the support of the Department of Ambulatory Care at Bellevue Hospital and the expert advice of consultants in the Departments of Medicine, Dermatology, Neurology, Surgery, and Psychiatry at New York University School of Medicine.

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1 Alcohol problems
Ann Morrison and Daniel Pomerantz

Epidemiology
- Alcohol is by far the most commonly used drug in the US.
- In 1992, 113 million people were current users of alcohol (44% of the US population 12 years and older), and about 8% of the population met criteria for alcohol abuse and dependence.¹
- The prevalence of alcohol problems in patients attending medical clinics is almost 20%.²
- The direct medical consequences of alcoholism include cirrhosis, cardiomyopathy, atrial fibrillation, pancreatitis, gastritis, dementia, and cancer of the esophagus, nasopharynx, liver, and (possibly) breast.

Definitions

Standards for alcohol intake
- A standard drink contains 12 grams of alcohol, equal to one 12-ounce bottle of beer, one 5-ounce glass of wine or 1.5 ounces of distilled spirits.

Safe use⁴
- Men under 65: <14 drinks per week, <4 drinks per occasion⁵
- Women and people over 65: <7 drinks per week, <3 drinks per occasion

At-risk use (also called hazardous use)
- Consumption of more than “safe” amounts

Harmful use (includes alcohol abuse)
- Evidence of medical or psychosocial consequences of alcohol use

Dependence
- Harmful use accompanied by three of the following symptoms of addiction:
  — tolerance
  — withdrawal
  — inability to cut down
  — sacrificing work, family or social events to drink
  — devoting a lot of time to finding and consuming alcohol
  — persistent drinking despite health problems.

Screening and diagnosis
- The outpatient setting is an ideal place to screen for alcohol abuse because of the high number of problem drinkers who come to their physicians for a variety of reasons.
- Physicians detect about three quarters of their patients who meet DSM-IV criteria for alcohol abuse or dependence, but only one third of problem drinkers.² Therefore, it is important

⁴ This definition for safe use comes from the National Institute on Alcohol Abuse and Alcoholism. Several, but not all, cohort studies show that odds ratios for mortality start to rise with consumption of between two and three drinks per day. However, the relationship between alcohol consumption and mortality is complex. The literature is well summarized in Reference 3.
⁵ Hindmarch I, Kerr JS, Sherwood N. The effects of alcohol and other drugs on psychomotor performance and cognitive function. Alcohol and Alcoholism 1991; 26:71–9. Recommendations for drinks per occasion are based on decline in psychomotor function with increasing consumption.
to use a validated screening tool routinely in questioning patients about their alcohol use.

The CAGE questionnaire

C: Have you ever felt you ought to CUT DOWN on your drinking?
A: Have people ANNOYED you by criticizing your drinking?
G: Have you ever felt bad or GUILTY about your drinking?
E: Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover? (EYE OPENER)

- A positive screen is a “yes” answer to any two questions. Any “yes” answer requires detailed follow up questioning.
- The operating characteristics of the CAGE questionnaire in one outpatient setting were as follows:

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- The implication of these results is that a “yes” answer to three or four questions is virtually diagnostic of alcohol abuse or dependence, while four “no” answers makes alcohol abuse or dependence highly unlikely.
- Other studies have found sensitivities and specificities ranging from 77–97% for detecting alcohol abuse or dependence. But the CAGE questions are far less effective at detecting drinking at the harmful or hazardous levels (sensitivity of 14–69%).
- The questionnaire should always be used in conjunction with questions about quantity and frequency of alcohol consumed in order to detect at-risk drinkers.
- The CAGE questions do not perform as well in women, ethnic minorities, and the elderly.
- The AUDIT (Alcohol Use Disorder Identification Test) is a 10-item questionnaire for early identification of hazardous and harmful drinkers. It was developed by the World Health Organization specifically for use in multicultural populations. The maximum possible score is 40, and a score of 8 or more is considered positive.
- The AUDIT is a better tool than the CAGE for detecting hazardous or harmful drinkers (sensitivity 57–95%, specificity 78–96%) and does not appear to be affected by ethnicity or race. It has not been tested in the elderly. Because it consists of 10 questions, it is more cumbersome than the CAGE, but it can be self-administered.
**Symptoms and signs suggesting alcohol problems**
- Insomnia, irritability, depression, anxiety
- Ill-defined somatic complaints: abdominal pain, headaches, low back pain
- Poorly controlled hypertension
- Trauma
- Lab abnormalities: macrocytosis, thrombocytopenia, elevated transaminases (especially γ-glutamyltransferase), amylase, and HDL-cholesterol
- Problems at work or school, driving while intoxicated

**Treatment**
- Traditionally, physicians have focused on the treatment of alcohol dependence and its medical complications. Usually this takes place in the inpatient setting. This population can be the most difficult and recalcitrant to treat.
- The National Institute on Alcohol Abuse and Alcoholism (NIAAA) recommends early intervention with drinkers of hazardous and harmful amounts of alcohol in order to prevent medical and social complications.\(^{11}\) These patients usually present to their physicians in outpatient settings with other medical complaints.
- While hazardous and harmful drinking behavior may not be detected in a typical office visit, these patients are usually more amenable to change than alcohol-dependent inpatients.

**Goals of treatment**
- **Controlled drinking** (cutting down to safe levels) may be sufficient for some drinkers of hazardous and even harmful amounts of alcohol.\(^ {12}\)
- **Complete abstinence** is recommended for patients who:
  - are alcohol dependent
  - have failed trials of controlled drinking repeatedly in the past
  - have medical consequences of alcohol abuse
  - are pregnant.

**Counseling by the physician**
- Primary care physicians can be effective in assisting heavy drinkers who are not yet alcohol dependent to reduce alcohol consumption through brief interventions.\(^ {13,14}\)
- Brief interventions consist of one or more 10–15 minute counseling sessions aimed at moderation.
- Patients receiving brief interventions have shown improvement in clinical markers, such as GGT and diastolic BP, and in clinical endpoints, such as hospitalizations and mortality.\(^ {15}\)

**The FRAMES model of brief interventions**
- The FRAMES model is a counseling style which is motivational\(^ {16}\) rather than confrontational. Confrontation...
has been associated with higher levels of alcohol consumption at one-year follow up.17

- The important components of brief interventions are summarized in the following acronym.18
  
  **Feedback:** “I’m concerned about your drinking because of your stomach and blood pressure problems.”
  
  **Responsibility:** “You’re the only person who can decide to stop drinking for a while to see what will happen.”
  
  **Advice:** “I think it would be best for you to stop drinking altogether for the next two weeks, so that we can see if it helps.”
  
  **Menu:** “Many people find it helpful to speak with a social worker or counselor, while others might prefer to check in with me several times over the next two weeks. You might also consider attending groups like Alcoholics Anonymous or our Alcohol Clinic.”
  
  **Empathy:** “I know it will be difficult for you not to drink, because it helps you unwind. But I’m concerned about the problems you’re having.”
  
  **Self-efficacy:** “It will be difficult for you not to drink, but I think your willingness to talk openly about your drinking and to set goals for yourself will help you to stop.”

- The use of visual aids such as educational pamphlets, drinking diary cards for patients to chart their consumption, and written prescriptions to “cut down on your drinking” have also been found to be important components of brief interventions.19 These can be obtained from the NIAAA. (See the list of resources at the end of the chapter.)

- Brief interventions that incorporate follow up sessions appear to be more successful than single session interventions.20

- The goal of a brief intervention is to moderate drinking. In most cases they are not appropriate for patients who are already alcohol dependent.

- In the case of patients who are alcohol dependent, the role of the primary care physician is to motivate the patient to seek more intensive care. The FRAMES model described above can be adapted for this purpose.

### Pharmacotherapy

#### Detoxification

- The goals of detoxification are to prevent potential morbidity and mortality from alcohol withdrawal and, secondarily, to facilitate the patient’s entry into a treatment program.

- The severity of withdrawal can be graded as mild, moderate or severe based on the Clinical Institute Withdrawal Assessment.21

- Traditionally, detoxification has taken place only in the inpatient setting. However, for patients with mild to moderate withdrawal, outpatient detoxification can be as effective as inpatient detoxification.22

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Outpatient detoxification can be considered for the following patients:\(^\text{23}\):

- less than 65 years of age
- mild to moderate withdrawal
- consuming < 12 drinks per day
- no previous history of withdrawal seizures, delirium or psychosis
- medically and psychologically stable
- stable, drug and alcohol free home environment, not living alone
- commitment to a treatment plan involving professional help, regular follow up and abstinence from all mood altering drugs.

Patients receiving outpatient detoxification must be evaluated daily until signs and symptoms of withdrawal are minimal and a formal rehabilitation program has begun.

Benzodiazepines are the only agents which have been shown to prevent withdrawal seizures and delirium tremens in physically dependent alcoholics.\(^\text{24}\)

Longer acting benzodiazepines, such as chlordiazepoxide, have less abuse potential but slower onset and more risk of oversedation than shorter acting agents such as lorazepam.

Medication is more effective when it is begun early.

A standard fixed dose regimen is chlordiazepoxide (Librium) 50 mg PO q6h 4 doses tapered to 25 mg PO q6h until withdrawal symptoms subside.

Alternatively, medication can be given only as needed (symptom trigger administration). This can decrease the duration of treatment and the total amount of medication administered,\(^\text{25}\) but has not been studied in the outpatient setting.

### Relapse prevention

- Once patients have achieved sobriety after detoxification, relapse is common (up to 70% in the MATCH trial – see reference 32). Relapse prevention is an important component of alcohol treatment.
- Medications that decrease craving for alcohol by blocking its pleasurable effects on the brain have only been studied as adjuncts to counseling.\(^\text{26}\)

### Medications for relapse prevention

- Naltrexone (50 mg/day) is an antagonist of endogenous opioids. Naltrexone has been shown to decrease relapse rates and drinking frequency.\(^\text{27}\)
- Acamprosate (1300–2000 mg/day) is believed to interact with the γ-aminobutyric acid (GABA) system. It has shown some benefits\(^\text{28}\) but is not available in the US.
- Serotonergic agents have generally not been found to be effective in non-depressed patients. Fluoxetine showed benefit in one small study with depressed patients.\(^\text{29}\)

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\(^{27}\) Volpicelli JR, Rhines KC, Rhines JS, Vocigelli LA, Alteman AF, O’Brien CP. Naltrexone and alcohol dependence: role of subject compliance. Arch Gen Psychiatry 1997;54:737–42. 97 patients were randomized to naltrexone or placebo in addition to counseling. Of the 73% of patients who were compliant with therapy, the naltrexone group had significantly less relapse (NNT=4).


\(^{29}\) Cornelius JR, Salloum IM, Ehler JG, et al. Fluoxetine in depressed alcoholics: a double-blind, placebo-controlled trial. Arch Gen Psychiatry 1997;54:700–5. 51 patients with major depression were assigned to fluoxetine or placebo in addition to weekly psychotherapy. Patients on fluoxetine showed significant improvement in all measures of alcohol use, but did not show a significant improvement in abstinence.
Disulfiram (Antabuse)
- Disulfiram (Antabuse) (250–500 mg/day) acts as an aversive agent. It blocks the metabolism of alcohol, resulting in the accumulation of acetaldehyde, making the consumption of alcohol an unpleasant experience. When patients taking disulfiram consume alcohol they experience flushing, headache, nausea and vomiting.
- The literature is mixed on whether disulfiram is effective or no better than placebo in relapse prevention.\textsuperscript{30,31} It likely has a role in a select group of patients in conjunction with psychosocial counseling.
- Disulfiram is contraindicated in patients with cardiovascular disease, suicidal ideation, hypothyroidism, pregnancy or patients on MAO inhibitors or antihypertensive medication.
- Adverse reactions include optic neuritis, polyneuropathy, and acute psychosis.

Referral
- Referral for specialty treatment is always appropriate for patients who are alcohol dependent.
- For patients who are harmful or hazardous drinkers, referral can be beneficial for those who are willing.
- There is a wide array of alcohol treatment services available. Studies have shown small differences between treatment modalities.\textsuperscript{32} Often, treatment selection will be based on local availability and the patient’s financial resources and insurance.
- More than a third of patients with alcohol disorders have coexistent psychiatric diagnoses.\textsuperscript{33} Psychiatric referral can be of benefit in treating these comorbid issues, but psychotherapy has not been found to be an effective treatment for alcohol abuse.

Alcoholics Anonymous (AA)
- The most widely available treatment. Although AA does not keep membership rolls, there are roughly 1.2 million members in the US. It is free.
- The guiding principles of AA are that alcoholism is a disease and that the only treatment is abstinence. AA also encourages spiritual renewal through belief in a “higher power”.
- Because AA does not routinely participate in research, data on its efficacy are primarily anecdotal. A meta-analysis\textsuperscript{34} of studies (many of poor methodological quality) evaluating the effectiveness of AA found a moderate relationship between AA attendance and improved psychosocial function and reduced alcohol intake.
- The peer support provided by AA can be a powerful tool in motivating drinkers to abstain. Many patients in stable recovery report that AA was an essential part of their recovery.
- Patients can be referred to either “open” or “beginner” meetings. Physicians can attend AA meetings as observers.


\textsuperscript{32} Project MATCH Research Group. Matching alcoholism treatments to client heterogeneity: project MATCH three-year drinking outcomes. Alcohol Clin Exp Res 1998;22:1300–11. 952 mainly alcohol dependent outpatients were assigned to cognitive behavioral therapy motivational enhancement therapy, or 12-step facilitation. At three years, 29% were abstinent in all groups. Those who were not completely abstinent drank less.

\textsuperscript{33} Regier DA, Farmer ME, Rae DS et al. Comorbidity of mental disorders with alcohol and other drug abuse: results from the epidemiologic catchment area (ECA) study. JAMA 1990;264: 2511–18.

Some patients find the religious premise of AA to be a barrier. Other self-help groups are Moderation Management, Rational Recovery, and Women for Sobriety.

**Resources**
- The National Institutes of Health/National Institute on Alcohol Abuse and Alcoholism (www.niaaa.nih.gov) has useful patient and physician education materials.
- The National Clearinghouse of Drug and Alcohol Information (www.health.org) offers manuals on topics such as screening, brief interventions, and motivation.
- Alcoholics Anonymous (www.alcoholics-anonymous.org)
2 Anemia
Dina Chenouda

Epidemiology
- Anemia is a marker of disease and can be associated with increased mortality.1
- Iron deficiency is the commonest cause of anemia worldwide and is frequently encountered in both hospital and general practice. It is usually secondary to inadequate dietary replacement of iron lost from the body.
- The daily iron requirement for men and non-menstruating women is 1.0 mg. Menstruating women require 2–3 mg. Pregnant women require 3–4 mg.2
- About 10% of menstruating teenagers and women have iron deficiency. True iron deficiency anemia is seen in 2.5%. Less than 1% of young men have iron deficiency anemia. Two percent of men and women over the age of 70 have iron deficiency anemia.3
- Routine screening for anemia in non-pregnant, asymptomatic patients is generally not recommended. Screening may be reasonable in pregnant women because iron deficiency anemia is common and can be related to poor fetal outcomes.3

Clinical presentation
- The clinical presentation of anemia depends on the abruptness of onset, severity, age, and ability of cardiopulmonary system to compensate for decrease in blood volume and oxygen carrying capacity.
- Anemia symptoms tend to be non-specific. They include fatigue, dyspnea, palpitations, and vague abdominal or chest discomfort. Signs include pallor, skin atrophy (angular stomatitis, glossitis, brittle nails), and tachycardia.

Diagnosis and evaluation
- While physical exam can suggest anemia,4 it is usually only helpful in cases that are severe5 and/or abrupt in onset (for example, hemorrhage with altered vital signs). In practice, most anemias are diagnosed by laboratory testing.

Complete blood count with RBC indices
- Hemoglobin (Hb) and hematocrit (Hct) identify the presence and severity of anemia.
- Mean corpuscular volume (MCV) reflects average RBC volume. MCV < 80fl indicates microcytosis. MCV > 100fl indicates macrocytosis.
- Random distribution width (RDW) is the range of RBC volumes. RDW increases with presence of different sized cells (macrocytes and microcytes). Normal is 14–16%.

Normal Hemoglobin and Hematocrit Values

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Hb (g/dl)</th>
<th>Hct (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premenopausal women</td>
<td>13–17</td>
<td>41–53</td>
<td></td>
</tr>
<tr>
<td>Postmenopausal women</td>
<td>11–15</td>
<td>34–46</td>
<td></td>
</tr>
</tbody>
</table>

1 Izaks GJ, Westendorp RGJ, Knook DL. The definition of anemia in older persons. JAMA 1999;281:1714–17. In this 10-year community-based study of 1016 elderly patients (≥ 85 years), anemia was associated with a 1.6 RR of all-cause mortality.


4 Sheth TN, Choudhry NK, Bowes M, Detsky AS. The relation of conjunctival pallor to the presence of anemia. J Gen Intern Med 1997;12:102–6. In this prospective evaluation of 202 inpatients, presence of conjunctival pallor had a +LR = 4.5 for severe anemia (Hb ≤ 9).

Peripheral blood smear
- Changes in individual cell diameter, shape, and hemoglobin content can precede changes in the RBC indices.
- Specific RBC morphologies are associated with specific disease states.

Reticulocyte count
- The reticulocyte count is a measure of RBC production. Normally, 1–2% of circulating RBCs are reticulocytes. This percentage increases in anemia, provided there is adequate iron and functioning bone marrow. It should be corrected for the patient’s hematocrit.

Measures of iron stores
- Ferritin is an indirect measure of total body iron. Men have larger iron stores (ferritin = 50–150 micrograms/ml) than women (15–50 micrograms/ml). Low ferritin levels correspond to iron deficiency. High levels are seen in hemochromatosis. Ferritin may be non-specifically increased in many inflammatory states as an acute phase reactant.
- Definitive evaluation of iron stores is made by bone marrow biopsy (see below).
- Iron (Fe) and total iron binding capacity (TIBC) reflect iron metabolism. Normally, only 30–50% of transferrin is bound with iron. Transferrin saturation (Fe/TIBC ratio) decreases in iron deficiency.

Bone marrow aspiration and biopsy
- Bone marrow examination allows evaluation of erythroid (as well as myeloid and platelet) maturation and assessment of total iron stores.
- Indications for aspiration and biopsy include:
  - anemia with inappropriately low reticulocyte count
  - pancytopenia
  - presence of immature or atypical cells on peripheral smear
  - anemia unexplained by other, less invasive tests.

Other tests
- Erythropoietin is elevated in most anemias, except in the setting of renal failure.
- Hemoglobin electrophoresis patterns can distinguish the hemoglobinopathies (thalassemias, sickle cell disease).

Microcytic anemias (MCV <80 fl)
Iron deficiency
Etiology
- Inadequate intake
- Inadequate absorption
- Excessive blood loss

RBC morphologies and disease states
- Sickle cells: sickle cell anemia
- Schistocytes: disseminated intravascular coagulation, thrombotic thrombocytopenic purpura
- Spherocytes: hereditary spherocytosis, autoimmune hemolytic anemia
- Teardrop cells: bone marrow fibrosis, myeloid metaplasia, malignancy
- Burr cells: uremia
- Target cells: thalassemia, liver disease
- Acanthocytes: severe liver disease

Corrected reticulocyte count
Reticulocyte count × hematocrit (%)

<table>
<thead>
<tr>
<th>Ferritin (micrograms/ml)</th>
<th>LR</th>
<th>Diagnostic impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15</td>
<td>52</td>
<td>Rule in</td>
</tr>
<tr>
<td>15–34</td>
<td>5</td>
<td>Intermediate high</td>
</tr>
<tr>
<td>35–64</td>
<td>1</td>
<td>Indeterminate</td>
</tr>
<tr>
<td>65–94</td>
<td>0.4</td>
<td>Intermediate low</td>
</tr>
<tr>
<td>≥95</td>
<td>0.08</td>
<td>Rule out</td>
</tr>
</tbody>
</table>

Microcytic anemias
- Iron deficiency
- Thalassemias
- Sideroblastic anemia
- Aluminum or lead toxicity
- Anemia of chronic disease (rarely)
Menstruation, peptic ulcer disease, and colon cancer are the most common causes in developed countries. Helminthic diseases are a significant cause in developing countries.

**Laboratory evaluation**

- Ferritin is the single most useful test. The probability of iron deficiency decreases with increasing levels. Low values (< 15 micrograms/l) are diagnostic of iron deficiency anemia. High values (> 100 micrograms/l) rule out iron deficiency.
- Decreased serum iron and increased TIBC cause a fall in transferrin saturation (Fe/TIBC ratio). In practice, these tests only add information when the ferritin level is non-diagnostic.
- Bone marrow aspiration is only required when the diagnosis is not clear from standard blood tests.
- Iron deficiency anemia in men and non-menstruating women necessitates an evaluation of the GI tract. Most clinicians do not pursue an extensive work up in asymptomatic menstruating women, but this has not been rigorously studied.
- Because anemia is a late sign of iron deficiency, there is evidence that iron deficiency in the absence of anemia (in non-menstruating women) warrants similar evaluation.

**Treatment**

- Oral iron supplementation with ferrous sulfate or ferrous gluconate is the most common form of treatment. Absorption is improved in an acidic state, so concomitant vitamin C or orange juice is often recommended. However, in the setting of iron deficiency the gastric mucosa is iron avid, so there is little benefit from additional acid.
- All agents that reduce gastric acid (calcium, antacids, H₂ blockers, proton pump inhibitors) decrease iron absorption.
- Side effects from oral iron are common and include nausea, constipation, diarrhea, and abdominal pain. Food can minimize these side effects, but can also decrease absorption. Changing to a different preparation may help. Up to 20% of patients discontinue iron supplementation because of its side effects. Weekly administration may be as effective as daily iron.
- Reticulocytosis should be apparent within 7–10 days. The hemoglobin should increase by about 3 g per month. Once the ferritin has reached 50 micrograms/dl, iron supplementation should continue for at least three months to fully replenish stores. Patients with low dietary intake or chronic blood loss require continuous maintenance therapy.
- Parenteral iron may be indicated in patients with malabsorption or inability to tolerate oral iron. Clinical response times are the same as with oral supplements. Intramuscular iron dextran must be administered under supervision because of the risk of anaphylaxis. Other side effects include headache, dyspnea, flushing, nausea, vomiting, fever, hypotension, and seizures.
• Dialysis patients receiving erythropoietin often respond better to intravenous iron therapy.\textsuperscript{10}

Thalassemia
• The thalassemias are genetic disorders of globin chain synthesis.
• \(\beta\) thalassemia is characterized by insufficient \(\beta\) chain production, with resultant increase in \(\alpha\) chains. Homozygous mutations (\(\beta\) thalassemia major or Cooley’s anemia) result in severe clinical illness with transfusion dependence or death if untreated.
• Heterozygous mutations (\(\beta\) thalassemia minor or \(\beta\) thalassemia trait) are generally asymptomatic. This is characterized by mild anemia but significant microcytosis. There is an increase in hemoglobin A\(_2\) and F seen on hemoglobin electrophoresis.
• \(\beta\) thalassemia is common in persons of Greek and Italian descent, but it is also seen in blacks and Southeast Asians.\textsuperscript{11}

<table>
<thead>
<tr>
<th>(\beta) Thalassemia Syndromes</th>
<th>Hb</th>
<th>MCV</th>
<th>Hb A (%)</th>
<th>Hb A(_2) (%)</th>
<th>Hb F (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>12–17</td>
<td>80–100</td>
<td>97–99</td>
<td>1–3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>(\beta) thal minor</td>
<td>9–11</td>
<td>50–70</td>
<td>80–95</td>
<td>4–8</td>
<td>1–5</td>
</tr>
<tr>
<td>(\beta) thal intermedia</td>
<td>7–10</td>
<td>50–70</td>
<td>0–30</td>
<td>0–10</td>
<td>6–10</td>
</tr>
<tr>
<td>(\beta) thal major</td>
<td>2–7</td>
<td>50–70</td>
<td>0–10</td>
<td>4–10</td>
<td>90–96</td>
</tr>
</tbody>
</table>

• \(\alpha\) thalassemia results in excess production of \(\beta\) chains. The clinical manifestations depend on how many of the four \(\alpha\) loci are affected. If only one (silent carrier) or two (\(\alpha\) thalassemia minor or \(\alpha\) thalassemia trait) loci are affected, there are no clinical manifestations. With \(\alpha\) thalassemia minor, there is mild anemia with significant microcytosis.
• If three (hemoglobin H disease) or four (hydrops fetalis) loci are affected, the resultant hemolytic anemia can be severe. Hydrops fetalis is uniformly fatal.
• \(\alpha\) thalassemias have an increased frequency in blacks, American Indians, and Asians.
• \(\alpha\) thalassemias are diagnosed by DNA analysis.

<table>
<thead>
<tr>
<th>(\alpha) Thalassemia Syndromes</th>
<th># of affected loci</th>
<th>Hb</th>
<th>MCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0</td>
<td>12–17</td>
<td>80–100</td>
</tr>
<tr>
<td>Silent carrier</td>
<td>1</td>
<td>12–17</td>
<td>80–100</td>
</tr>
<tr>
<td>(\alpha) thal minor</td>
<td>2</td>
<td>10–13</td>
<td>60–70</td>
</tr>
<tr>
<td>Hb H disease</td>
<td>3</td>
<td>8–10</td>
<td>60–70</td>
</tr>
<tr>
<td>Hydrops fetalis</td>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

• Transfusion is the treatment of choice for the clinically significant thalassemias (\(\beta\) thalassemia intermedia or major
and hemoglobin H disease). Chronic transfusion runs the risk of iron overload and iron chelation therapy is often needed.\textsuperscript{12}

- Splenectomy is often helpful in patients with high transfusion requirements.
- Bone marrow transplantation may be an option in selected patients, but mortality is high.\textsuperscript{13}

**Sideroblastic anemia**

- Sideroblastic anemia is a group of disorders of red cell maturation. It can be idiopathic (part of a myelodysplastic syndrome) or drug induced. Chloramphenicol, antituberculosis agents, alcohol, and lead can cause sideroblastic anemia.
- Ringed sideroblasts (immature red cells with a ring of stain around the nucleus) are seen on bone marrow biopsy.

**Normocytic anemias (MCV 80–100 fl)**

**Anemia of chronic disease (ACD)**

**Etiology**

- ACD is caused by the inability of the bone marrow to utilize available iron for heme synthesis. This may be because of iron trapping by activated macrophages and/or suppression of erythropoiesis by inflammatory cytokines (interleukin, tumor necrosis factor, prostaglandin).\textsuperscript{14}
- It is usually associated with chronic inflammatory diseases, malignancy or chronic infections (HIV, osteomyelitis, endocarditis), but may be seen with any illness.

**Laboratory evaluation**

- Although ACD may become marked, it is usually non-progressive, with Hb levels remaining above 9 g/dl.
- On blood smear, erythrocytes are normocytic or mildly microcytic. Often the peripheral smear is nearly normal.
- Iron and TIBC are both decreased; ferritin is increased.
- The marrow iron stores are usually normal or increased.
- Erythropoietin levels are often low.

**Treatment**

- The treatment of ACD is directed at the underlying cause. Iron therapy is of no benefit.
- In patients with low erythropoietin levels, exogenous erythropoietin administration can be helpful.\textsuperscript{15}
- Anemia of chronic renal insufficiency is due to impaired production of erythropoietin. In addition to exogenous erythropoietin administration, patients require iron supplementation to a target ferritin of >100 mg/dl because bone marrow stores are rapidly depleted. Iron is often given intravenously in this situation.\textsuperscript{16}

\textsuperscript{12} Olivieri NF, Nathan DG, MacMillan JH et al. Survival in medically treated patients with homozygous \( \beta \) thalassemia. \textit{N Engl J Med} 1994;331:574–8. In a cohort of 97 patients treated with transfusion and chelation therapy, maintenance of ferritin <2500 mg/dl was the strongest predictor of survival.


\textsuperscript{14} Means RT. Advances in the anemia of chronic disease. \textit{Int J Hematol} 1999;70:7–12.

\textsuperscript{15} Henry DH. Recombinant human erythropoietin treatment of anemic cancer patients. \textit{Cancer Practice} 1996;4:180–4. Treatment with erythropoietin may decrease the need for transfusion. There are only small clinical trials.

**Aplastic anemia**

- Aplastic anemia is an acquired bone marrow defect of all cell lines. Etiologies include viruses (HIV, hepatitis B or C, cytomegalovirus, Epstein-Barr) and drugs (chloramphenicol, sulfa, gold, carbamazepine). Many cases are idiopathic.
- It is characterized by pancytopenia and ineffective reticulo-cytosis. Treatment involves immunosuppressive therapy. Bone marrow transplantation may be required.

**Macrocytic anemias (MCV > 100 fl)**

**Vitamin B₁₂ (cobalamin) deficiency**

- Vitamin B₁₂ deficiency is usually a result of malabsorption, since body stores of vitamin B₁₂ are sufficient for up to five years. Malabsorption can be caused by pernicious anemia, gastrectomy, intestinal parasites, bacterial overgrowth, pancreatic insufficiency, ileitis or ileal resection. Most vitamin B₁₂ comes from animal sources, so strict vegetarians may have dietary insufficiency.
- Clinical manifestations include ataxia, paresthesias, numbness, ataxia, dementia, psychosis, and a smooth, beefy-red tongue. Neurological symptoms can occur in the absence of anemia.¹⁷
- Higher MCV (>110 fl) is more suggestive of B₁₂ deficiency. Peripheral smear may show hypersegmented neutrophils.¹⁸ Megaloblasts can be seen in the bone marrow.
- Serum vitamin B₁₂ concentration is easily measured. Methylmalonic acid and homocysteine reflect vitamin stores and are elevated in vitamin B₁₂ deficiency, even in the face of normal serum levels.¹⁹ Only homocysteine is elevated in folate deficiency (see below).
- Pernicious anemia, the most common cause of vitamin B₁₂ deficiency in the Western world, has traditionally been evaluated with the Schilling test and antibodies to intrinsic factor and parietal cells. These tests are not specific,²⁰ however, and the diagnosis of pernicious anemia does not alter the treatment of B₁₂ deficiency.

**Treatment**

- Intramuscular, oral or intranasal preparations are available for vitamin B₁₂ replacement. Because most deficiencies are due to malabsorption, the oral form is usually insufficient.
- Daily injections of 1000 micrograms of cyanocobalamin are given for the first week, followed by weekly injections for 4–6 weeks. Monthly maintenance injections of 1000 micrograms are usually required for life.
- Hematologic improvement occurs within 1–2 weeks. Symptoms of anemia improve rapidly, but neurological symptoms can take months. Some neurological deficits are permanent.
- An intranasal gel (Nascobal) has recently been approved as maintenance therapy for patients already treated and in

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remission. Weekly administration provides 500 micrograms of cobalamin.

Folate deficiency
- Dietary insufficiency is a common reason for folate deficiency, since total body stores of folate are easily depleted in several months. Inadequate intake of folate is often seen in alcoholics, elderly people, and teenagers.
- Malabsorption (especially sprue) can lead to folate deficiency.
- Increased folate requirements with insufficient intake can be seen in pregnancy, malignancy, and hemodialysis.
- Drug therapy with folate antagonists can cause folate deficiency.
- Vegetables, fruits, dairy products, and cereals are the most important sources of folate. Some forms of folate are labile and destroyed during cooking.
- Clinical manifestations include malnourishment, cheilosis, and glossitis. There are no neurological symptoms.
- Hematologic alterations (MCV > 110, hypersegmented neutrophils, bone marrow megaloblasts) are the same as with vitamin B12 deficiency.
- Serum folate levels reflect recent intake and therefore may be normal despite depleted total body stores. Red cell folate, a more accurate indicator, is not subject to such fluctuations.
- Homocysteine levels are elevated in folate deficiency, but methylmalonic acid is normal.18

Treatment
- Oral supplementation of folate (1 mg daily) replenishes body stores in about three weeks. If there is an element of malabsorption, 5 mg daily may be required, but parenteral administration is rarely necessary.
- Because exogenous folate can partially correct the hematological abnormalities (though not the neurological symptoms) of vitamin B12 deficiency, serum B12 levels should be assessed prior to folate therapy.
- Folate supplementation of 0.4 mg daily is recommended for women of childbearing age to reduce the incidence of fetal neural tube defects.21

Myelodysplasia
- Myelodysplastic syndromes (or pre-leukemic syndromes) are acquired disorders of ineffective stem cell maturation. Typically, the bone marrow is normocellular or hypercellular, but these cells are dysplastic. This impaired hematopoiesis leads to peripheral pancytopenia.
- The etiology may be related to genetic defects, radiation, chemicals (benzene, alkylating agents), and aplastic anemia.
- Early myelodysplasia may be asymptomatic or may present with the non-specific symptoms of anemia.

Folate antagonists
- Methotrexate
- Pyrimethamine
- Trimethoprim
- Triamterene
- Sulfasalazine
- Oral contraceptives
- Anticonvulsants
- Alcohol

21 Berry RJ, Li Z, Erickson JD et al. Prevention of neural-tube defects with folic acid in China. China–U.S. Collaborative Project for Neural Tube Defect Prevention. N Engl J Med 1999;341:1485–90. This public health campaign evaluated the infants of 130,000 women who took folate and 118,000 who did not. Neural tube defects were found in 102 and 118, respectively. The greatest decrease, 85%, was seen in the subgroup of women who were compliant with therapy (> 80% of pills) and lived in areas with the highest risk of neural tube defects.
• Progression to acute leukemia varies from 5–50% depending on morphological classification.
• Diagnosis is made by bone marrow biopsy with cytogenetic analysis.
• Curative treatment with bone marrow transplantation is only available for patients under 55 with histocompatible donors.
• Supportive therapy with periodic transfusion is the mainstay of treatment. There is some response to chemotherapeutic agents that suppress leukemic clones.

Hemolytic anemias
Sickle cell disorders
• The term encompasses the range of disorders for which at least one sickle gene has been inherited.
• Heterozygous sickle cell trait is usually clinically silent, with normal red cell indices. Rarely, symptoms will present during severe hypoxia (for example, at high altitude). Nearly 10% of blacks carry this trait, which can be detected on hemoglobin electrophoresis demonstrating 40% HbS.
• True sickle cell anemia (homozygous sickle genes or SS disease) is characterized by chronic hemolysis and vaso-occlusive crises from the sickled red cells. Complications include aseptic necrosis of bone and infarction of the spleen, brain, lungs or kidneys. Other forms of sickle cell disease (hemoglobin SC disease and sickle cell/β thalassemia) can have similar clinical presentations. The distinctions between them are mainly important for genetic counseling.
• Prevention of sickle cell crisis is the major goal of therapy. Immunization against pneumococcus, hepatitis B, and influenza is recommended. Patients should avoid precipitants such as hypoxia and dehydration. Supplementation with folate is generally given.
• Treatment of sickle cell crisis involves hydration and pain relief. Transfusions do not affect the course of a typical painful crisis and are usually given only for neurological events, priapism, preparation for surgery, and acute chest syndrome with hypoxia.
• The acute chest syndrome consists of chest pain, leukocytosis, pulmonary infiltrates, and hypoxia. It is unclear whether there is an infectious component, but broad spectrum antibiotics are usually administered because infection cannot be ruled out.
• Hydroxyurea increases production of fetal hemoglobin, which does not sickle under hypoxic conditions. This decreases the number of painful vaso-occlusive episodes. Because of the unknown effects of chronic treatment, particularly in children, hydroxyurea is generally reserved for those patients with frequent and severe painful crises including acute chest syndrome and other vaso-occlusive events.


24 Charache S, Terrin ML, Moore RD et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. N Engl J Med 1995;332:1317–22. 299 patients were randomized to hydroxyurea or placebo. The trial was terminated early at 21 months because of a decrease in number of painful crises (2.5 v 4.5 per year) and time to first crisis (3.0 v 1.5 months). There were also fewer episodes of acute chest syndrome and transfusion.
Bone marrow transplantation is potentially curative, but its use is limited by complications and the lack of suitable donors.

**Glucose-6-phosphate dehydrogenase (G6PD) deficiency**

- In the absence of sufficient G6PD, red blood cells are subject to hemolysis under antioxidant stresses. G6PD deficiency is an X-linked trait.
- Mild forms are seen in up to 10% of black men. Typically there are no symptoms unless the patient is exposed to oxidizing drugs (especially sulfa and antimalarial) or infections.
- More severe forms are seen in Mediterranean populations. Hemolysis classically occurs upon ingestion of fava beans.
- Diagnosis can be made by measuring G6PD levels, but they may be normal after a hemolytic episode, since immature cells contain more G6PD than the older, more recently hemolyzed cells.
- Treatment involves avoidance of precipitants and adequate hydration during hemolytic episodes.

**Autoimmune hemolytic anemia (AIHA)**

- Autoantibodies to red cells cause intermittent hemolysis.
- Warm IgG antibodies can be idiopathic, drug induced or related to underlying malignancy or chronic inflammatory disease.
- Symptoms include weakness, jaundice, and splenomegaly.
- Diagnosis can be made by showing specific IgG, as well as elevated LDH and decreased haptoglobin.
- Hemolysis is treated with glucocorticoids or splenectomy, but the underlying cause must be addressed.
- Cold AIHA is characterized by cold induced peripheral cyanosis. The antibody is a paraprotein associated with underlying malignancy or infection (especially mycoplasma or Epstein-Barr).

**Indication for blood transfusion**

- Use of absolute hemoglobin levels in the decision to transfuse appears to be less helpful than the evaluation of tissue oxygenation status.
- In acute anemia, a rapid blood loss of more than 30% (or Hb < 6 g/dl) usually justifies transfusion.
- In chronic anemia, transfusion may be required in symptomatic patients who are unresponsive to other therapies.
- In sickle cell disease and thalassemias, transfusion may prevent complications, although it does not affect the course of painful sickle crises.
- Perioperative mortality increases with anemia and is of concern for patients who decline transfusion and those with sickle cell disease.

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Drugs of concern with G6PD deficiency

- Sulfamethoxazole
- Dapsone
- Hydroxychloroquine
- Primaquine
- Nitrofurantoin
- Pyridium
- Hydralazine
- Vitamin K (water-soluble form)
- Doxorubicin

26 Hebert PC, Wells G, Blajchman MA et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. N Engl J Med 1999;340:409–17. 838 ICU euv-ICU patients with Hb < 10 g/dl were randomized to a restrictive (goal: Hb 7–9) or liberal (goal: 10–12) transfusion strategy. There was no difference in 30 or 60 day mortality or number of organ failures.


### Table 2.1  Agents for anemia.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage forms</th>
<th>Usual dosage (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous gluconate</td>
<td>325 mg tabs</td>
<td>300 mg PO tid</td>
</tr>
<tr>
<td>Ferrous sulfate</td>
<td>325 mg tabs</td>
<td>300 mg PO tid</td>
</tr>
<tr>
<td>Folic acid</td>
<td>1 mg tabs</td>
<td>1 mg PO qd</td>
</tr>
<tr>
<td></td>
<td>1000 micrograms/ml</td>
<td>1000 µg IM every 6 days × six doses, then...</td>
</tr>
<tr>
<td>Cyanocobalamin</td>
<td></td>
<td>1000 µg IM q 3 months for life</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>2000–20 000</td>
<td>Initially: 50–100 U/kg 3 times weekly IV or SC</td>
</tr>
<tr>
<td>(Epogen, Procrit)</td>
<td>units/ml</td>
<td>Titrate to target hematocrit</td>
</tr>
</tbody>
</table>
3 Anticoagulation
Danielle Ofri

Atrial fibrillation (AF) Recommendations
- All patients with AF in the presence of definite risk factors (see below) or mitral stenosis or prosthetic valves: warfarin, target INR of 2.5 (range 2.0–3.0).
- All patients >75 years: warfarin, target INR of 2.5 (range 2.0–3.0).
- All patients <65 years without risk factors: aspirin (ASA).
- Patients 65–75 years or those with moderate risk factors: individual decision: weigh risks/benefits and patient preference. Multiple moderate risk factors favors use of warfarin.
- Patients with paroxysmal AF: warfarin, target INR of 2.5 (range 2.0–3.0).

Benefit of anticoagulation
- Numerous large randomized controlled trials (RCTs) have shown definitive evidence that anticoagulation with warfarin reduces the rate of stroke compared to control INR or aspirin (data summary).\(^2\)
- For every 100 patients with AF who are anticoagulated with warfarin, an average of 3–5 strokes are prevented each year (RRR = 68%\(^3\) [CI = 50–79%], ARR = 3.1%). This is one of the most effective interventions ever documented for prevention of strokes.

Comments
- AF is the most common indication for long term anticoagulation.
- US\(^4\) and UK\(^5\) outpatient analyses indicate that 4–5% of people over the age of 65 have AF. This corresponds to 2.2 million Americans with AF and this number is expected to increase by 60% in the next 20 years. Nearly half of the patients who would benefit from anticoagulation are not receiving it.
- Risk of stroke ranges from 1–8% per year, with increased risk associated with age and additional (additive) risk factors.
- The definition of “lone AF” varies greatly; treatment should be based on presence of risk factors.
- High risk factors: previous TIA or stroke or thromboembolic (TE) event, hypertension, heart failure (clinical CHF or diminished ejection fraction), rheumatic mitral valve disease, prosthetic valve,\(^6\) age >75.
- Moderate risk factors: diabetes, coronary artery disease with normal ejection fraction, age 65–75.
- Non-valvular AF accounts for 80% of all cases. Valvular AF (mainly rheumatic) has a greater than threefold risk of stroke compared with non-valvular AF, but the recommendations for anticoagulation are the same.
Valvular heart disease

Recommendations
- Warfarin (target INR of 2.5, range 2.0–3.0) for mitral valve disease in the presence of AF, any TE event, left atrial diameter greater than 5.5 cm, severe stenosis, or heart failure.7
- Anticoagulation is not routinely recommended for aortic valve disease, mitral valve prolapse, mitral annular calcification, patent foramen ovale, or atrial septal aneurysm unless there is a documented thromboembolic event or the patient has AF.

Benefit of anticoagulation
There is no RCT data for valvular disease in the absence of AF.

Prosthetic valves
Recommendations
- The ACCP8 recommends a target INR of 3.0 (range 2.5–3.5) for most metal valves.
- An alternative recommendation is warfarin with target INR of 2.5 (range 2.0–3.0) plus ASA 80–100 mg.
- A lower target INR of 2.5 (range 2.0–3.0) is permissible for the subset of bileaflet or tilting disk valves in the aortic position with a normal size atrium, sinus rhythm, and normal ejection fraction.9
- Stronger anticoagulation may be needed for the older caged ball and caged disk valves.
- Consider adding ASA 80–100 mg to warfarin (target INR 3.0, range 2.5–3.5) for high risk patients (prior TE event, mitral prosthetic valve plus AF, coronary disease, enlarged atria, atrial thrombus, multiple mechanical valves).
- For bioprosthetic valves, anticoagulation with warfarin for target INR of 2.5 (range 2.0–3.0) is recommended for the first three months only. Lifelong anticoagulation is needed if there is associated AF.

Benefit of anticoagulation
- There are no RCTs comparing anticoagulation to placebo, only cohort studies.
- The benefits of anticoagulation are inferred by the high natural rate of thromboembolic events in untreated patients and the lower rate observed in anticoagulated patients.
- Thromboembolic events are more common with mechanical prostheses in the mitral (22%/year) than the aortic (12%/year) position.10 These event rates drop to 1.4–3.0%/year with warfarin anticoagulation.11,12

Comments
- Older mechanical valves (caged ball, caged disk) are more thrombogenic than newer valves. Almost all prosthetic valves today are St Jude (bileaflet).
- There is some interest in combining antiplatelet agents with warfarin, with the hope of further lowering the thrombotic

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8 Stein PD, Alpert JS, Bussey HI, Dalen JE, Turpie AG. Antithrombotic therapy in patients with mechanical and biological prosthetic heart valves. ACCP-VI: 220S–8S.
9 Acar J, Iung B, Boissel JP et al. AREVA: A multicenter randomized comparison of low-dose versus standard-dose anticoagulation in patients with mechanical prosthetic heart valves. Circulation 1996;94:2107–12. In this prospective trial of mainly aortic bileaflet valves (in setting of normal atria, normal ejection fraction and sinus rhythm) 188 patients were randomized to INR 2–3 and 192 to INR 3–4.5. Over a mean of 2.2 years TE events were the same (9 v 10), but bleeding episodes were fewer (34 v 56) in the less intensively treated group.
complication rate and/or permitting a lower dose of warfarin to be used.\textsuperscript{13}

- Bioprosthetic (porcine) valves in either the aortic or mitral position have low rates of thromboembolism (comparable to mechanical valves with anticoagulation), except in the first three months after placement.\textsuperscript{14}

- Anticoagulation is only necessary for prosthetic valves in the mitral and aortic positions, though the aortic tends to be less thrombogenic than the mitral.

- Frequently, INRs are found to be 1.0 during routine follow up. There is no consensus (and certainly no randomized studies) regarding the best approach in this situation. Expert opinion ranges from immediate hospitalization for intravenous heparin, outpatient treatment with subcutaneous unfractionated or LMW heparin, or simply restarting warfarin. The decision depends on the patient’s history of previous thromboemboli, how recently the valve was placed (highest rates of thrombosis are in the first three months, particularly in the first 10 days), the location and type of valve, and the patient’s other risk factors.

Deep venous thrombosis (DVT) and pulmonary embolus (PE)

Recommendations for treatment of DVT and PE

- For acute proximal vein DVT (popliteal or proximal) and PE, treat with low molecular weight heparin (LMWH) or IV unfractionated heparin (1.5–2.5 times PTT control) for at least five days to prevent extension of clot.\textsuperscript{15} Begin warfarin therapy on day 1 at estimated maintenance dose (usually 5 mg qd). When INR is 2.0–3.0 for at least three days, the heparin can be stopped.\textsuperscript{16}

- Warfarin should be continued for at least six months with a target INR of 2.5 (range 2.0–3.0), except perhaps in selected cases of reversible causes (see below).

- Isolated calf vein thrombi can be treated with anticoagulation or be followed with serial ultrasound (up to two weeks); anticoagulation should be instituted as above if signs of proximal extension are noted.

Recommendations for prevention of DVT and PE

- After the first TE event, oral anticoagulation with warfarin should be continued for at least six months,\textsuperscript{17} although in certain instances of specific, known precipitants (for example, trauma, surgery, estrogen use, transient immobilization), three months may be adequate.

- Patients with permanent risk factors (malignancy; homozygous activated protein C resistance; antiphospholipid antibody syndrome; deficiencies of antithrombin III, protein C or S) should receive at least 12 months, if not lifelong anticoagulation (target INR of 2.5, range 2.0–3.0).\textsuperscript{18}

\textsuperscript{13} Meschengieser SS, Fondevila CG, Frontroth J, Santorelli MT, Lazzari MA. Low-intensity oral anticoagulation plus low-dose aspirin versus high-intensity oral anticoagulation alone: a randomized trial in patients with mechanical prosthetic heart valves. J Thorac Cardiovasc Surg 1997;113:910–16. 258 patients were randomized to warfarin INR 2.5–3.5 plus 100 mg aspirin, and 245 patients to warfarin INR 3.5–4.5. After 23 months of prospective follow up, there was no difference in TE events or bleeding complications.


• For heterozygous activated protein C resistance and a first TE event, anticoagulation for 3–6 months may suffice.
• For a second DVT, indefinite anticoagulation is associated with an eight-fold decrease in TE events (20.7% to 2.6%).

Benefits of anticoagulation
• The benefit of extended warfarin treatment for thromboembolic events was demonstrated by a randomized open trial of six weeks versus six months of anticoagulation. About nine confirmed recurrent thromboembolic events were prevented per 100 patients treated for six months (ARR = 6.9% v 8.6% in one study\textsuperscript{22} and 5.3% v 6.7% in another\textsuperscript{21}). Major bleeding was similar (0.5% v 2%, and 2% v 1%).
• A recent Cochrane review concluded that LMWH was at least as effective as unfractionated heparin and was associated with less major hemorrhage and decreased overall mortality.\textsuperscript{22}

Comments
• LMWH is 10–20 times more expensive than unfractionated heparin. Since it is administered subcutaneously without need for laboratory monitoring, it can be used in the outpatient setting. The avoidance of hospitalization makes it cost effective.\textsuperscript{23}
• There is also excellent evidence for the effectiveness of LMWH treatment of PE,\textsuperscript{24,25} although it is not yet approved by the FDA for outpatient treatment.

Myocardial infarction (MI)
The use of aspirin for prevention of MI in CAD is well established, but the magnitude of benefit is far greater for secondary prevention than for primary prevention and greatest for acute MI.

Recommendations
• Aspirin 325 mg PO qd for acute MI, prior MI, or CAD.
• Consider aspirin (81 or 325 mg) for men (and possibly women) >50 in the presence of other cardiac risk factors: hypertension, hyperlipidemia, smoking, or (especially) diabetes.
• In the absence of definitive data,\textsuperscript{26} most clinicians do not routinely prescribe warfarin post-MI except in the case of a large anterior wall infarction or LV thrombus. Therapy is usually for three months (INR target = 2.0–3.0).

\textsuperscript{26} Coumadin Aspirin Reinfarction Study Investigators. Randomized double-blind trial of fixed low-dose warfarin with aspirin after myocardial infarction. Lancet 1997;350:389–96. The CARS trial (double-blinded RCT, 8823 patients) showed no benefit of fixed dose warfarin (1 and 3 mg) above and beyond that of aspirin in post-MI patients.
Benefit of ASA in primary prevention

- In the Physicians’ Health Study, about two MIs were prevented for every 1000 healthy men treated with aspirin for one year (RRR = 44%, ARR = 0.18%/year).\(^\text{27}\) There was a non-significant increase in hemorrhagic stroke and no difference in overall or cardiovascular mortality. The benefit was only seen in men over the age of 50 and was especially pronounced in those with diabetes. The main shortcoming of this trial was the low number of endpoint events (see also British Doctors’ Trial\(^\text{28}\)).

Benefit of ASA in secondary prevention

- The Antiplatelet Trialists’ Collaboration, in a summary of 11 secondary prevention trials, estimated that 36 vascular events (MI, CVA, or cardiovascular death) would be prevented by treating 1000 patients who have a history of MI with antiplatelet agents (usually aspirin) for two years (RRR = 24%, ARR = 2%/year).\(^\text{29}\)

Benefit of ASA in acute MI

- For acute MI, 38 events would be prevented by treating 1000 patients with aspirin for one month (RRR = 29%, ARR = 4%/month).\(^\text{29}\)

Heart failure

Recommendations

- The European Heart Association\(^\text{30}\) and the American Heart Association/American College of Cardiology\(^\text{31}\) suggest that anticoagulation may be helpful in selected patients with very low EF (20–25%) or with intracardiac thrombus (Class II recommendation).

Benefit of anticoagulation

- There are no RCTs supporting the use of warfarin in heart failure.
- Estimates of thromboembolic complications in heart failure range from 0.9–5.5 events per 100 patient-years and these tend to be associated with lower ejection fractions.\(^\text{32}\)

Cerebrovascular disease

Recommendations

- ASA 50–325 mg qd for prior stroke or TIA and possibly for acute stroke.
- Alternatives: clopidogrel (75 mg qd), ticlopidine (250 mg bid) or dipyridamole (long acting, 200 mg bid) plus ASA (50 mg).

Benefit of ASA in primary prevention

- Aspirin does not appear to be effective in primary prevention of stroke, as demonstrated by the slight increase in strokes seen in both the Physicians’ Health Study\(^\text{27}\) and the British Doctors’ Trial.\(^\text{28}\)

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\(^{28}\) Peto R, Gray R, Collins R et al. Randomised trial of prophylactic daily aspirin in British male doctors. BMJ 1988;296:313–16. The British Doctors’ Trial showed no decrease in MI or mortality with aspirin as primary prophylaxis. Although this was a large randomized trial, it was not blinded and there was no placebo used in the control group. Both primary prevention trials of aspirin enrolled men only. The Nurses’ Health Study, a prospective cohort of female nurses, demonstrated a RRR of 32% for first MI, but no differences in stroke or mortality. Manson JE, Stampfer MJ, Colditz GA et al. A prospective study of aspirin use and primary prevention in cardiovascular disease in women. JAMA 1991;266: 521–7.


Benefit of ASA in secondary prevention
- The Antiplatelet Trialists’ Collaboration, in a summary of 18 secondary prevention trials, estimated that 40 vascular events (MI, CVA, or cardiovascular death) would be prevented by treating 1000 patients who have a history of TIA or stroke with antiplatelet agents (usually aspirin) for three years (RRR = 18%, ARR = 1.3%/year).

Benefit of ASA in acute stroke
- In two large (20,000 patients each) RCTs in which aspirin therapy was initiated at the time of acute ischemic stroke, nine deaths or recurrent strokes were prevented at four weeks, with two additional intracranial bleeds, per 1000 patients treated. At discharge or six months, there were 13 fewer deaths or cases of dependency.

Comments
- Doses of aspirin in these trials ranged from 30–1500 mg per day, with little difference in efficacy, but no direct comparisons of low and high doses. Based on the kinetics of aspirin action on platelets, 75–100 mg is probably sufficient, but some experts feel that 975–1300 mg is more efficacious.
- Clopidogrel (Plavix) and ticlopidine (Ticlid) are two other antiplatelet agents that are at least as effective as aspirin for secondary prevention, but are far more expensive. Ticlopidine use is limited by the serious side effect of neutropenia. These agents are used when patients cannot tolerate aspirin.
- Dipyridamole (Persantine) in combination with aspirin may be more effective than aspirin alone.
- There is no evidence that warfarin provides any additional benefit over antiplatelet agents in secondary prevention. It is generally used when patients cannot tolerate, or have failed, antiplatelet therapy (recurrent stroke).

Practical aspects of anticoagulation and antiplatelet therapy

Warfarin
Overview
- Warfarin interferes with post-translational modification of clotting factors II, VII, IX and X, and anticoagulant proteins C and S. Factor VII and protein C have the shortest half-lives (six hours) and therefore are functionally depleted fastest.
- Warfarin can be initiated without concomitant heparin unless immediate anticoagulation is needed. The full anticoagulant effect of warfarin takes 3–4 days to become apparent, when the activity of factors II, IX, and X are affected.

Initiating anticoagulation
- If the patient is receiving intravenous unfractionated heparin or LMWH, warfarin can be started on day 1.

35 Albers GW, Amarenco P, Easton JD, Sacco RL, Teal P. Antithrombotic and thrombolytic therapy for ischemic stroke. ACCP-VI: 300S–20S.
Heparin is discontinued after INR is therapeutic for at least three days. Otherwise, initiation of warfarin for heparinized and unheparinized patients is the same.

- The estimated warfarin maintenance dose should be started immediately. Check PT on day 3 (after two doses), and then 2–3 times/week for the first two weeks. If INR is therapeutic, check PT weekly for the next two weeks, bi-weekly for the next two months, then monthly thereafter.
- Average maintenance dose is 4–5 mg per day. Expect a lower maintenance dose for elderly patients, patients with liver disease, and patients with malabsorption (of vitamin K).

The estimated warfarin maintenance dose should be started immediately. Check PT on day 3 (after two doses), and then 2–3 times/week for the first two weeks. If INR is therapeutic, check PT weekly for the next two weeks, bi-weekly for the next two months, then monthly thereafter.

Average maintenance dose is 4–5 mg per day. Expect a lower maintenance dose for elderly patients, patients with liver disease, and patients with malabsorption (of vitamin K).

The hypothetical procoagulant state caused by depletion of C is only an issue with protein C deficiency or activated protein C resistance syndromes.

Some clinicians initiate warfarin therapy with a bolus at twice maintenance dose, though this rarely achieves therapeutic INR any faster and may increase the risk of bleeding.

### Table 3.1  Summary of indications for anticoagulation and antiplatelet therapy.

<table>
<thead>
<tr>
<th>Clinical indication</th>
<th>Warfarin target INR</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation, &gt;75, or any age with risk factors</td>
<td>2.0–3.0</td>
<td>Indefinite</td>
</tr>
<tr>
<td>Atrial fibrillation, &lt;65, no risk factors (“lone”)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation, 65–75 years, or those with moderate risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitral stenosis/regurgitation with left atrial enlargement or failure</td>
<td>2.0–3.0</td>
<td>Indefinite</td>
</tr>
<tr>
<td>Mitral annular calcification</td>
<td>No anticoagulation</td>
<td></td>
</tr>
<tr>
<td>Native valve endocarditis</td>
<td>No anticoagulation</td>
<td></td>
</tr>
<tr>
<td>Bioprosthetic (porcine) valves</td>
<td>2.0–3.0</td>
<td>3 months post-op</td>
</tr>
<tr>
<td>Mechanical valves (current generation bileaflet and tilting disk)</td>
<td>2.5–3.5 or 2.0–3.0+</td>
<td>Indefinite</td>
</tr>
<tr>
<td>Consider adding ASA 80–100 mg for high risk patients</td>
<td>ASA 80–100 mg</td>
<td></td>
</tr>
<tr>
<td>Bileaflet valves in aortic position with normal atrium, sinus rhythm, and normal</td>
<td>2.0–3.0</td>
<td>Indefinite</td>
</tr>
<tr>
<td>ejection fraction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Older valves (caged ball and caged disk)</td>
<td>2.5–3.5 + ASA (80–100 mg)</td>
<td>Indefinite</td>
</tr>
<tr>
<td>First DVT/PE</td>
<td>2.0–3.0</td>
<td>6 months</td>
</tr>
<tr>
<td>First DVT with heterozygous activated protein C resistance</td>
<td>2.0–3.0</td>
<td>6 months</td>
</tr>
<tr>
<td>Recurrent DVT or first DVT with any other permanent risk factor</td>
<td>2.0–3.0</td>
<td>Indefinite</td>
</tr>
<tr>
<td>Post-MI – severe anterior wall or LV thrombus</td>
<td>2.0–3.0</td>
<td>? 3 months</td>
</tr>
<tr>
<td>Ejection fraction &lt;25% + LV thrombus</td>
<td>2.0–3.0</td>
<td>? Indefinite</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>2.0–3.0</td>
<td>Indefinite</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>ASA 325 mg qd</td>
<td>Indefinite</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>ASA 325 mg qd or</td>
<td>Indefinite</td>
</tr>
<tr>
<td></td>
<td>clopidogrel 75 mg qd</td>
<td></td>
</tr>
<tr>
<td></td>
<td>or ticlopidine 250 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>bid or dipyridamole</td>
<td></td>
</tr>
<tr>
<td></td>
<td>400 mg sustained</td>
<td></td>
</tr>
<tr>
<td></td>
<td>release + ASA 50 mg</td>
<td></td>
</tr>
</tbody>
</table>
Maintaining anticoagulation (see Table 3.2).

- There are several published algorithms for warfarin adjustments, though many clinicians adjust warfarin doses based on intuition and experience.

- Regarding the frequent adjustment of warfarin doses: it is easier for the patient to take the same dose every day, but in some cases it is more feasible to alternate doses (by dividing the pills) to avoid the necessity of having many different pill strengths.

- Before a dose is automatically altered on the basis of a non-therapeutic INR, first inquire about changes in diet and other medications (including over the counter medications, herbs, and vitamins). Too often this is ignored and unnecessary dose changes and blood testing ensue, leading to further patient confusion and non-compliance.

Complications of warfarin therapy (see Table 3.3)

- Hemorrhage rates increase with higher INRs, more variable INRs, and initiation of warfarin therapy (higher in the first three months). The literature is in disagreement as to whether advanced age is an independent risk factor.\(^{39}\)

  Various studies report an annual incidence of major bleeding (predominantly GI) of 1–4% per year; fatal bleeds 0.2–0.1% per year.\(^{40}\)

- Warfarin induced skin necrosis is rare (0.001% of warfarin treated patients) and usually occurs within the first 3–6 days of therapy.

Interactions with warfarin

- Many drugs affect warfarin’s biological activity.\(^{41}\) When a new drug is added, the INR should be monitored 2–3 times per week. The most common drugs that prolong the INR are antibiotics, H\(_2\) blockers, sulfonylureas, and NSAIDs.


\(^{40}\) Levine MN, Raskob G, Landefeld S, Kearon C. Hemorrhagic complications of anticoagulant treatment. ACCP-VI: 108S–21S.


Table 3.2  Warfarin adjustments for target INR of 2–3.

Example dose: 5 mg PO qd.

<table>
<thead>
<tr>
<th>INR</th>
<th>Day 1 adjustment</th>
<th>Maintenance dose adjustment</th>
<th>Check INR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1–1.4</td>
<td>Double dose (10 mg)</td>
<td>Increase 10–20% (6 mg)</td>
<td>1 week</td>
</tr>
<tr>
<td>1.5–1.7</td>
<td>Increase 50% (7.5 mg)</td>
<td>Increase 5–10% (5/6 mg alternating)</td>
<td>2 weeks</td>
</tr>
<tr>
<td>1.8–1.9</td>
<td>No change</td>
<td>No change</td>
<td>1 week</td>
</tr>
<tr>
<td>2–3</td>
<td>No change</td>
<td>No change</td>
<td>4 weeks</td>
</tr>
<tr>
<td>3.1–3.2</td>
<td>No change</td>
<td>No change</td>
<td>1 week</td>
</tr>
<tr>
<td>3.3–3.9</td>
<td>Decrease 50% (2.5 mg)</td>
<td>Decrease 5–10% (4/5 mg alternating)</td>
<td>2 weeks</td>
</tr>
<tr>
<td>4–4.9</td>
<td>No warfarin</td>
<td>Decrease 10–20% (4 mg)</td>
<td>1 week</td>
</tr>
<tr>
<td>5–5.9</td>
<td>Hold</td>
<td>Decrease 20–50% after INR = 3 (3 mg)</td>
<td>Daily until INR = 3</td>
</tr>
</tbody>
</table>
Selected medications that affect INR (level I and II evidence)

**Increased INR**: alcohol, amiodarone, steroids, cimetidine, erythromycin, fluconazole, INH, metronidazole, omeprazole, miconazole, propranolol, piroxicam, acetaminophen, ASA, chloral hydrate, ciprofloxacin, quinidine, phenytoin, tetracycline, flu vaccine

**Decreased INR**: barbiturates, carbamazepine, chlordiazepoxide, cholestyramine, nafcillin, rifampicin, sucralfate, enteral feeds, dicloxacillin

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**Table 3.3 Managing complications of warfarin therapy.**

<table>
<thead>
<tr>
<th>INR</th>
<th>Symptom</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>6–10</td>
<td>No bleeding (or rapid reversal for surgery)</td>
<td>Vitamin K 1–2 mg SC; expect reduction within 8h. Many patients therapeutic in 24h. If still high, may give another 0.5 mg after 24h. Resume warfarin at lower dose.</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>No bleeding</td>
<td>Vitamin K 3 mg SC; expect reduction within 6h. Check INR at 6h and repeat vitamin K if necessary.</td>
</tr>
<tr>
<td>&gt; 20</td>
<td>Serious bleeding or major warfarin overdose</td>
<td>Vitamin K 10 mg SC plus fresh frozen plasma or prothrombin concentrate depending on urgency. Check INR every 6h. May repeat vitamin K every 12h.</td>
</tr>
</tbody>
</table>

(including ASA). The most common drugs that decrease the INR are oral contraceptives and antacids.

- Patients must be instructed about consistent dietary intake of foods containing vitamin K. This advice is commonly misinterpreted as to avoid vegetables altogether. The foods highest in vitamin K are leafy greens, broccoli, and brussel sprouts.

**Aspirin**

- Aspirin permanently inactivates platelet cyclo-oxygenase, thereby inhibiting thromboxane A₂. Platelet aggregation is inhibited for the lifetime of the platelet (seven days). Thromboxane A₂ is also a potent vasoconstrictor.
- Aspirin should be taken with food to minimize GI side effects.
- Patients taking aspirin have a 40–60% increased incidence of nausea, heartburn, and stomach pain. The most serious risk is hemorrhage (GI 1–5%, CNS approximately 0.3% in various trials). It is not clear whether these side effects are dose dependent.⁴²
- As a NSAID, aspirin can increase the risk of chronic renal failure. Aspirin sensitivity may be an issue with asthmatic patients. Other effects include tinnitus and attenuated response to antihypertensives.

**Clopidogrel, ticlopidine and dipyridamole**

- Clopidogrel and ticlopidine irreversibly inhibit platelet aggregation by blocking the adenosine diphosphate pathway. The mechanism of dipyridamole is not fully understood.
- These drugs are metabolized by the liver and should be taken with food to minimize GI side effects.
- Diarrhea and skin rash are the most common side effects of clopidogrel and ticlopidine (20% and 12% in one study).³⁷

Neutropenia, the most serious side effect, occurs in 1–3% of patients.

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patients taking ticlopidine (but not clopidogrel). Frequent hematologic monitoring is recommended (every two weeks for the first three months of ticlopidine use). Dipyridamole may cause dizziness and headache.

**Unfractionated heparins**
- Unfractionated heparin is a naturally occurring glycosaminoglycan normally present in human tissue. It binds to antithrombin III, promoting the inactivation of thrombin and Factor Xa.
- Unfractionated heparin may be administered as a continuous IV infusion for treatment of TE events and unstable angina. In the outpatient setting, it can be administered by subcutaneous injection, usually for TE prophylaxis or during pregnancy (for example, with a prosthetic valve when warfarin is contraindicated).

**Low molecular weight heparins (LMWH) (see Table 3.4)**
- LMWH molecules are depolymerized from unfractionated heparin. They are more uniform in size and have more predictable pharmacokinetics. They can be dosed according to weight and do not require INR checks. Additionally, they are less antigenic and cause much less thrombocytopenia than unfractionated heparin.
- LMWH is given subcutaneously and is metabolized by the kidney. Dosing must be adjusted in renal failure.
- The various forms of LMWH are not biologically equivalent. Dosing is different and results in clinical trials of one form cannot be extrapolated to another.

**Perioperative issues (see Table 3.5)**
- Warfarin is usually stopped four days before surgery to allow the INR to drop to 1.5; this is considered a safe level at which to operate. Warfarin is restarted immediately post-op and a therapeutic INR can be achieved within three days. Because of the partial protection afforded by even subtherapeutic INRs, the patient is really without anticoagulation only one day pre-op and one day post-op. Since surgery itself increases the risk of thromboemboli, the first post-op day is the most dangerous.43
- Elective surgery should be avoided in the first month following a venous or arterial thrombosis.
- Antiplatelet agents should be discontinued 7–10 days pre-op.
- LMWH should be discontinued one day pre-op.
- IV heparin should be discontinued four hours pre-op.

**Special situations**
**Elderly patients**
- The SPAF trials indicated that elderly patients with atrial fibrillation are at increased risk for stroke and receive the greatest benefit from anticoagulation. However, this

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population is the least likely to have warfarin appropriately prescribed. Advanced age may not be an independent risk factor for bleeding.

- It may be prudent to avoid warfarin in patients with increased risk of falls or who are unable to comply with therapy.
- There are no specific contraindications to antiplatelet or heparin therapy in elderly patients.

Pregnancy
- Warfarin is a pregnancy category X drug (known teratogen) and should not be used during pregnancy or lactation. Female patients of childbearing age who require warfarin therapy should be strongly counseled about birth control. Subcutaneous heparin or LMWH are typically used during pregnancy.

Table 3.4  Indications and dosages for low molecular weight heparin.

<table>
<thead>
<tr>
<th>LMWH</th>
<th>DVT prophylaxis for surgery (first dose usually given several hours prior to surgery)</th>
<th>DVT treatment</th>
<th>Unstable angina, NQWMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
<td>Hip/knee† 30 mg q12 h Abdominal 40 qd</td>
<td>Inpatient (+/− PE) 1 mg/kg q12 h or 1.5 mg/kg qd Outpatient (without PE) 1 mg/kg q12 h</td>
<td>1 mg/kg q12 h</td>
</tr>
<tr>
<td>(Lovenox)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dalteparin</td>
<td>Hip 5000 IU qd Abdominal 2500 IU qd Knee 50 IU/kg q12 h</td>
<td>Pending</td>
<td>120 IU/kg (max 10 000 IU) q12 h</td>
</tr>
<tr>
<td>(Fragmin)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ardeparin</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(Normiflo)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Danaparoid</td>
<td>Hip 750 IU/kg q12 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Orgaran)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3.5  Perioperative treatments for patients on long term warfarin.43
All patients stop warfarin four days before surgery and restart as soon as possible.

<table>
<thead>
<tr>
<th>Situation</th>
<th>Pre-op</th>
<th>Post-op</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute venous thromboembolism, month 1</td>
<td>IV heparin</td>
<td>IV heparin</td>
</tr>
<tr>
<td>Acute venous thromboembolism, month 2 or 3</td>
<td>−</td>
<td>IV heparin</td>
</tr>
<tr>
<td>Recurrent venous thromboembolism</td>
<td>−</td>
<td>SC heparin</td>
</tr>
<tr>
<td>Acute arterial thromboembolism, month 1</td>
<td>IV heparin</td>
<td>IV heparin</td>
</tr>
<tr>
<td>Mechanical heart valve</td>
<td>−</td>
<td>SC heparin</td>
</tr>
<tr>
<td>Non-valvular atrial fibrillation</td>
<td>−</td>
<td>SC heparin</td>
</tr>
</tbody>
</table>

There is some evidence that the teratogenic effects of warfarin occur mainly when the drug is administered between weeks 6 and 12. It may be not be as harmful in the first six weeks. Iurbe-Alessio I, Fonseca MC, Mutchinik O, Santos MA, Zajarias A, Salazar E. Risks of anticoagulant therapy in pregnant women with artificial heart valves. N Engl J Med 1986;315:1390–3.
Unfractionated heparin is category C. It is not excreted in breast milk.

All LMWH drugs are category B with the exception of ardeparin which is category C. It is not known if these drugs are excreted in breast milk.

Aspirin is a category D drug. At high doses in the third trimester there have been reports of fetal intracranial bleeding. But at least one large randomized trial and one well conducted meta-analysis have demonstrated the safety of low dose aspirin (60–150 mg qd) in the second and third trimesters. Salicylates are excreted in breast milk and should be avoided during lactation.

Clopidogrel, ticlopidine and dipyridamole are category B drugs. They (or their metabolites) are excreted in breast milk and should be avoided during lactation.

**New directions**

- In a recent double blind RCT of 933 patients undergoing total hip replacement, a synthetic indirect inhibitor of factor Xa was at least as efficacious as enoxaparin at preventing DVT. At higher doses, it was more effective. Synthetic agents are likely to gain increasing prominence.

- In an open label study of 1137 patients with DVT, reviparin (not yet FDA approved) was compared to unfractionated heparin. As measured by venography, thrombus regression occurred in 53 versus 43% of patients, respectively. Recurrence of DVT or PE occurred in 1.8–3.5% versus 6.4%. This suggests that LMWH may be superior to unfractionated heparin, and may become the recommended treatment in the near future.

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4 Arterial disease of the lower extremities
Lloyd Wasserman

Epidemiology
- The incidence of intermittent claudication is 15.5 per 1000 person-years.\(^1\)
- The incidence of chronic critical ischemia of the lower extremity is 0.5–1.0 per 1000 person-years.\(^2\)

Prevalence of Intermittent Claudication by Age and Sex\(^3\)

<table>
<thead>
<tr>
<th></th>
<th>30–39</th>
<th>40–49</th>
<th>50–59</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>0.6%</td>
<td>1.9%</td>
<td>4.6%</td>
</tr>
<tr>
<td>Women</td>
<td>1.1%</td>
<td>1.6%</td>
<td>2.8%</td>
</tr>
</tbody>
</table>

- More than 50% of patients with intermittent claudication are current smokers.\(^3\)
- In men with intermittent claudication aged 40–59, the RR of cardiovascular mortality is 2.6.\(^4^,\(^5\)

Diagnosis
Categories of arterial occlusive disease of the legs (AOD)
- **Non-critical lower extremity ischemia**: often presents as intermittent claudication. This represents non-limb threatening ischemia if the pattern is stable over time.
- **Chronic critical ischemia**: this is limb threatening ischemia that warrants urgent consultation with a vascular surgeon. It often presents as pain at rest.
- **Acute ischemia**: caused by embolic disease or in situ thrombosis; it requires urgent hospitalization for treatment.

History
- Risk factors for atherosclerosis, cardiovascular disease, cerebrovascular disease; medications; bleeding or thrombotic disorders.
- Symptoms: pain (location and onset), skin ulcers (usually in the distal forefoot), change in skin color, paresthesias, weakness, and differential temperature. In diabetic patients, neuropathy may alter or limit ischemic pain.

Syndromes of arterial occlusive disease
**Non-critical ischemia**
- The classic history is of intermittent claudication: calf pain during walking, worsened by hurrying or walking uphill, and relieved by standing still for <10 minutes.
- The prognosis for the limb is good. With a program of medical therapy and smoking cessation, few patients progress to arterial reconstruction or amputation.

\(^4\) Reunanen A, Takkunen H, Aromaa A. Prevalence of intermittent claudication and its effect on mortality. Acta Med Scand 1982;211:249–56. Structured interviews of 10,962 people aged 30–59 from 12 population groups in Finland. The RR of 2.6 was obtained after regression analysis for age, blood pressure, cholesterol, and smoking (P = <0.01).
\(^5\) Results of Coronary Angiography in Patients with Arterial Occlusive Disease of the Lower Extremities

<table>
<thead>
<tr>
<th>Coronary angiogram</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal vessels</td>
<td>10</td>
</tr>
<tr>
<td>Mild-moderate disease</td>
<td>33</td>
</tr>
<tr>
<td>Advanced compensated disease</td>
<td>29</td>
</tr>
<tr>
<td>Severe correctable disease</td>
<td>21</td>
</tr>
<tr>
<td>Severe inoperable disease</td>
<td>7</td>
</tr>
</tbody>
</table>

Atypical exertional pain is defined as exertional leg pain that does not affect the calves, is not worsened by hurrying uphill, or is not relieved by standing still for <10 minutes. Atypical symptoms are common among patients with AOD.

### Rates of Leg Symptoms in Patients With and Without Arterial Occlusive Disease

<table>
<thead>
<tr>
<th></th>
<th>AOD</th>
<th>No disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms</td>
<td>15%</td>
<td>77%</td>
</tr>
<tr>
<td>Atypical exertional pain</td>
<td>25%</td>
<td>5%</td>
</tr>
<tr>
<td>Intermittent claudication</td>
<td>31%</td>
<td>4%</td>
</tr>
<tr>
<td>Pain at rest</td>
<td>29%</td>
<td>14%</td>
</tr>
</tbody>
</table>

### Differential diagnosis

- **Pseudoclaudication**:  
  - Caused by nerve root compression secondary to narrowing of the spinal canal by bony or soft tissue elements.  
  - Patients have a history of back pain radiating to the buttock, thigh, and/or calf.  
  - Like claudication, the pain of pseudoclaudication is worse with walking; unlike claudication, it is not relieved by standing still.  
  - Activities that increase lumbar lordosis, such as walking downhill, worsen lumbar nerve root compression and increase the pain of pseudoclaudication; walking uphill may improve pseudoclaudication. True vascular pain is worsened when walking up an incline.

- **Deep venous thrombosis**: calf pain does not resolve with rest, but may improve with elevation of the lower extremities.

- **Nocturnal leg cramps**: are not associated with exertion. Dependent position does not alter the symptoms.

### Chronic critical ischemia

- **Rest pain** represents potentially limb threatening ischemia secondary to chronic arterial disease.  
  - Occurs when the patient is supine and is severe in intensity.  
  - The pain is usually located in the toes, distal forefoot, or heel.  
  - Symptoms improve with placement of the leg in a dependent position.

- **Ischemic ulcers** occur in the distal forefoot and heel. They are pale and exquisitely tender. Pain is worsened by leg elevation.

- Patients with rest pain or ischemic ulcer should be evaluated urgently by a peripheral vascular surgeon.

- Patients who are not candidates for arterial reconstruction should be educated about signs of infection, necrosis, and rapid progression that would require immediate evaluation.

---

McDermott MM, Mehta S, Greenland P. Exertional leg symptoms other than intermittent claudication are common in peripheral arterial disease. Arch Intern Med 1999;159:387–92. Prospective study of consecutive patients at one institution's blood flow laboratory diagnosed with AOD (ABI < 0.9). Their symptoms were compared against randomly selected patients with an upcoming general medical appointment and who were subsequently found to have normal ABI results (0.9–1.5). ABI = ankle brachial index (see below)
• Mortality and amputation rates are high in patients who have inoperable disease or are too ill to undergo surgical arterial reconstruction.

Probability of Mortality and Limb Loss Among Inoperable Patients With Chronic Critical Leg Ischemia

<table>
<thead>
<tr>
<th>Outcome</th>
<th>1 month (%)</th>
<th>3 months (%)</th>
<th>12 months (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>7</td>
<td>23</td>
<td>54</td>
</tr>
<tr>
<td>Amputation</td>
<td>19</td>
<td>30</td>
<td>46</td>
</tr>
<tr>
<td>Neither</td>
<td>71</td>
<td>56</td>
<td>28</td>
</tr>
</tbody>
</table>

Acute ischemia

• Blue toes syndrome: acute onset of cyanosis and patchy erythema of the toes due to atheroemboli.
  —Pedal pulses are often present.
  —There may be associated livedo reticularis (purplish, weblike discoloration of the skin) in the legs.
  —Patients may also have evidence of atheroemboli to other organs: kidneys, gastrointestinal tract, brain, or eye.
  —These patients warrant urgent referral to a vascular surgeon.

• Acute diffuse ischemia:
  —Presents with acute onset of pain and coldness of the limb.
  —Pallor occurs during the first few hours, with subsequent development of cyanosis.
  —There is progressive sensory and motor loss. Profound weakness and anesthesia represent irreversible tissue loss and usually require amputation.
  —Pulses are not detectable distal to the site of the occlusion.
  —The etiology can be embolic or thrombotic.
  —Adequate collateral circulation may mask the symptoms of acute thrombosis in patients with chronic AOD.
  —Emboli are usually symptomatic, particularly in patients without chronic AOD. Most emboli are of cardiac origin.
  —Patients with symptoms of acute arterial occlusion should be admitted to the hospital emergently for appropriate diagnosis of cardiac thromboembolism versus in situ thrombosis and treatment with thrombolysis or surgery.

Physical examination

• Examine for other manifestations of atherosclerotic disease.
• Patients with atherosclerotic risk factors or established arterial occlusive disease should have serial examinations of the carotid, brachial, radial, aortic, femoral, popliteal, dorsalis pedis, and posterior tibial arteries by palpation. Auscultate large vessels for bruits. Pulses should be described as normal, decreased, or absent (2+, 1+, or 0). Operating characteristics for the examination of the pedal pulses are described to the right.

Retrospective study of 105 patients and 136 limbs. Amputation rates listed to the left are per limb, not per patient.

Classic presentation of acute arterial occlusion: the Six Ps

• Pain
• Pallor
• Pulselessness
• Paresthesias
• Progression to paralysis
• Polar sensation (decreased limb temperature)

Rate of Palpable Dorsalis Pedis Pulse in Patients with Specific ABI Results and Clinical Syndromes

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Palpable DP(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABI &gt; 1.0</td>
<td>80</td>
</tr>
<tr>
<td>ABI ≤ 1.0</td>
<td>18</td>
</tr>
<tr>
<td>ABI &gt; 0.82</td>
<td>68</td>
</tr>
<tr>
<td>ABI ≤ 0.82</td>
<td>5</td>
</tr>
<tr>
<td>Claudication</td>
<td>27</td>
</tr>
<tr>
<td>Rest Pain</td>
<td>9</td>
</tr>
</tbody>
</table>

Retrospective study of 100 patients referred for lower extremity Doppler.

Interobserver Agreement: Palpation of Dorsalis Pedis and Posterior Tibialis Arteries

<table>
<thead>
<tr>
<th>Observer</th>
<th>Interobserver agreement (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular surgeons</td>
<td>53</td>
</tr>
<tr>
<td>Medical students</td>
<td>67</td>
</tr>
<tr>
<td>Vascular lab staff</td>
<td>82</td>
</tr>
</tbody>
</table>

Prospective study of nine examiners performing pulse exams on 25 patients. The authors speculate that the vascular lab staff may have had more time, as well as more peace and quiet, thus providing for greater accuracy in their exams.
Dependent rubor and pallor upon limb elevation suggest AOD.

Diagnostic testing

Ankle brachial index (ABI)
- The normal ratio of ankle systolic blood pressure to brachial blood pressure is >1. Systolic blood pressure in the lower extremity is normally ≤10 mmHg higher than in the upper extremity. An ABI <1 suggests AOD; a ratio of <0.5 is consistent with severe ischemia. ABI correlates with level of functional impairment.
- The accuracy of the test decreases in chronic renal failure, diabetes mellitus, obesity, vascular calcification, and systolic heart failure.
- Yearly ABI may help to assess prognosis in patients with symptoms or signs of AOD, particularly in diabetic patients who may not experience significant symptoms from advanced disease.

General Correlation of Single ABI Test Result to Symptoms and Extent of Disease

<table>
<thead>
<tr>
<th>Patient group</th>
<th>ABI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent claudication</td>
<td>0.5–0.8</td>
</tr>
<tr>
<td>Rest pain</td>
<td>≤0.3</td>
</tr>
<tr>
<td>Involvement of 1 arterial segment</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>Multisegmental involvement</td>
<td>≤0.5</td>
</tr>
</tbody>
</table>

Likelihood Ratios for Specific Outcomes in Arterial Occlusive Disease Based on Change in Serial ABI

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Decrease in ABI</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression of symptoms</td>
<td>≥0.15</td>
<td>1.8</td>
</tr>
<tr>
<td>Future surgical intervention</td>
<td>≥0.15</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Toe systolic blood pressure (TSBP)
- Useful when vessel wall calcification causes false negative ABI results (for example, in diabetes). Indicators of vessel wall calcification are ankle systolic BP >300 mmHg or ankle systolic BP >75 mmHg above brachial pressure.
- A TSBP index above 0.6 is considered normal.
- In the presence of a foot ulcer, a TSBP of 30 mmHg indicates that the ulcer is not likely to heal without vascular repair.

Arterial duplex mapping
- Useful for evaluating patients without a clear diagnosis following clinical assessment and ABI.
- Too labor intensive to be used routinely for all patients.
- May be used instead of an angiogram prior to angioplasty.
- Its use instead of angiography for preoperative assessment has not been validated.
- Angiography is necessary for elective operative planning.


Operating Characteristics of Diagnostic Tests for Arterial Occlusive Disease

<table>
<thead>
<tr>
<th></th>
<th>Stenosis (%)</th>
<th>Occlusion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duplex scan</td>
<td>80</td>
<td>95</td>
</tr>
<tr>
<td>Magnetic resonance</td>
<td>82</td>
<td>84</td>
</tr>
<tr>
<td>Percutaneous contrast</td>
<td>92</td>
<td>77</td>
</tr>
</tbody>
</table>

Treatment

Overall goals of treatment
- Prevent mortality from associated cardiovascular disease
- Prevent limb loss
- Reduce symptoms and increase ambulation

Medical therapy

Antiplatelet therapy
- Because of the >50% rate of advanced coronary disease among patients with arterial occlusive disease, antiplatelet therapy (aspirin, ticlopidine, or clopidogrel) should be given to all such patients. It lowers mortality from comorbid conditions and may slow progression of lower extremity atherosclerosis.
- Among patients with claudication who take antiplatelet agents instead of placebo, the RR of combined endpoints of MI, stroke, or vascular death is about 82%. The average ARR with antiplatelet therapy is about 2% over two years.12

Aspirin
- In patients on aspirin compared to placebo, the RR for progression of arterial stenoses to occlusions is 0.60. The ARR is 1.4% (as a percentage of lesions, not patients) over the course of two years.13
- Because it is inexpensive and there are no proven clinically significant differences between aspirin and other agents, aspirin is the antiplatelet agent of choice.

Ticlopidine
- When compared with placebo, ticlopidine is associated with a 7% ARR for death from ischemic heart disease in patients with intermittent claudication over a time period of 5.5 years.14
- Patients on ticlopidine may have longer pain free walking distance than those on placebo.15
- Because of the risk of neutropenia during the first three months of therapy, ticlopidine should be reserved for those who cannot tolerate aspirin.
- Patients require frequent monitoring of complete blood count.

References:
11 Baum RA, Rutter CM, Sunshine JH et al. for the American College of Radiology Rapid Technology Assessment Group. Multicenter trial to evaluate vascular magnetic resonance angiography of the lower extremity. JAMA 1995;274:875–80. In this study, the gold standard for contrast angiography and MRA was intraoperative contrast angiography (N = 155).
12 Antiplatelet Trialists' Collaboration. Collaborative overview of randomized trials of antiplatelet therapy. I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ 1995;308:81–106. In the table to the left, duplex scan appears more accurate than percutaneous angiogram, but this conclusion is not valid, as the two tests were measured against different gold standards. Duplex scan was measured against percutaneous angiogram itself; percutaneous angiogram was measured against intraoperative angiogram, an even better test. A gold standard is a test against which all other tests are measured. Ideally, it should have sensitivity and specificity of 100%, but this is rarely possible. Percutaneous angiogram is considered the gold standard for AOD, but as seen in the table, it is less than perfect.
**Clopidogrel**

- When compared with aspirin, there is a 24% RRR and a 1% per patient-year ARR in favor of clopidogrel for the composite endpoint of total MI, stroke, and fatal vascular events.
- There is no statistically significant difference between clopidogrel and aspirin for vascular and cardiovascular mortality.
- Although chemically related to ticlopidine, clopidogrel does not cause a significant incidence of cytopenias.

**Cilostazol**

- Inhibits platelet aggregation and increases vasodilation. Patients with intermittent claudication have a mean improvement of pain-free walking distance of 50% on 24 weeks of cilostazol, compared to 30% on placebo.17

**Pentoxifylline**

- Not an antiplatelet agent. Pentoxifylline improves blood flow by increasing the deformability of red blood cells.
- It may reduce symptoms and improve walking distance. Patients with intermittent claudication improve their pain-free walking distance on a treadmill 29.4 meters more than those on placebo.18

**Non-pharmacological treatment**

**Smoking cessation**

- Reduces the incidence of limb loss and improves exercise capacity.
- The RR of progression from claudication to critical ischemia is 2.6 for cigarette smokers when compared to ex-smokers or never-smokers. The ARR for never smoking or stopping smoking is 13%.19
- For patients who have a past surgical history of peripheral arterial reconstructive surgery, the RR of future amputation is 10 among heavy smokers (≥15 cigarettes/day) versus moderate or occasional smokers. The ARR for moderate versus heavy smoking is 19%.20

**Other recommended interventions**

- **Routine walking**: the target is 30–60 minutes, five days a week, at >2 miles per hour. Various controlled studies report an 88–190% increase over baseline in pain-free walking distance with walking exercise programs. Controls experience a 22% reduction to a 19% increase in pain-free walking distance.21
- The target LDL cholesterol level is 100 mg/dl. LDL cholesterol levels >130 mg/dl should be treated with an HMG-CoA reductase inhibitor.
- Appropriate control of diabetes and hypertension.
- **Foot care**: patients should examine their feet daily and have periodic evaluations by a podiatrist.

**References**


16. CAPRIE Steering Committee. A randomised, blinded trial of clopidogrel versus aspirin in patients at high risk of vascular events. Lancet 1996;348: 1329–39. Study of 19,185 patients with a history of MI, ischemic stroke, or AOD. The AOD subgroup had a greater RRR than the other subgroups.


20. Lassila R, Lepantalo M. Cigarette smoking and the outcome after lower arterial stenoses, randomized to placebo, aspirin, or aspirin and dipyridamole. The P values for differences between aspirin alone and placebo were >0.05.
• *Surgical consultation* should be obtained for progressive symptoms, severe limitation of activity, rest pain, gangrene, acute onset of ischemic symptoms, or ischemic ulcers.

21 Ernst E, Fialka V. *A review of the clinical effectiveness of exercise therapy for intermittent claudication.* Arch Intern Med 1993;153:2337–60. There are no well designed, large studies of exercise in arterial occlusive disease. The four studies of pain-free walking distance ranged from 9–42 patients each. All trials showed benefit of treatment over control.

### Table 4.1 Medications for peripheral vascular disease.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage form</th>
<th>Usual dosage</th>
<th>Adverse effects, comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>325 mg</td>
<td>325 mg PO qd</td>
<td>GI upset, bleeding</td>
</tr>
<tr>
<td>Ticlopidine (Ticlid)</td>
<td>250 mg</td>
<td>250 mg PO bid</td>
<td>Severe neutropenia (0.9%), bleeding, nausea, vomiting. Taken with food. Patients should be educated about the symptoms of neutropenia. Complete blood count every 2 weeks for 3 months.</td>
</tr>
<tr>
<td>Clopidogrel (Plavix)</td>
<td>75 mg</td>
<td>75 mg PO qd</td>
<td>Bleeding, rash. Neutropenia is rare.</td>
</tr>
<tr>
<td>Cilostazol (Pletal)</td>
<td>50 mg, 100 mg</td>
<td>100 mg PO bid</td>
<td>Headache, diarrhea, palpitations. Dose is 50 mg bid in patients taking ketoconazole, itraconazole, erythromycin, or diltiazem.</td>
</tr>
<tr>
<td>Pentoxifylline (Trental)</td>
<td>400 mg</td>
<td>400 mg PO tid</td>
<td>Dyspepsia, headache, dizziness (2%). Taken with food.</td>
</tr>
</tbody>
</table>
5 Asthma and chronic obstructive pulmonary disease
Jahangir Rahman

Asthma
Epidemiology
- In 1998, ~17 299 000 people had asthma in the US.
- In 1995, there were 5637 reported deaths from asthma in the US.
- Age adjusted mortality is higher and has increased faster in blacks (to 3.8 per 100,000 population) than in whites (1.3 per 100,000).
- Asthma prevalence increased 75% from 1980 to 1994.

Diagnosis
Clinical characteristics
- Episodes of wheezing, cough, and dyspnea – especially at night
- Waxing and waning symptoms
- History of heightened airway reactivity to exercise, cold air, air pollutants, URIs, allergens, emotional stress
- Reversible airway obstruction on pulmonary function tests
- Increased airway response to challenge by methacholine, cold air.

History and physical examination – important items
- Sensitizers: aspirin, pets, dust, smoking, foods, medications
- Associations: eczema, nasal polyps, family history of asthma, gastroesophageal reflux disease (GERD)
- Severity: frequency and severity of symptoms, night-time symptoms, response to treatment, clinical status between exacerbations, steroid use, frequency of ER visits, admissions, intubations
- Spirometry and/or pulmonary function testing to help assess severity and reversibility. PFTs are often normal in asthmatic people who are asymptomatic at the time (unless challenged with cold air or methacholine).

Treatment
Goals of asthma therapy
- Maintain a normal level of activity, including exercise.
- Maintain normal or near normal pulmonary function.
- Prevent troubling symptoms (for example, night-time dyspnea).
- Prevent recurrences.


2 National Center for Health Statistics

Asthma Prevalence by Age, 1995

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18</td>
<td>7.5%</td>
</tr>
<tr>
<td>18–44</td>
<td>5.2%</td>
</tr>
<tr>
<td>45–64</td>
<td>5.3%</td>
</tr>
<tr>
<td>≥65</td>
<td>4.0%</td>
</tr>
</tbody>
</table>

Differential diagnosis of asthma
- Chronic bronchitis
- Emphysema
- Occupational asthma
- Congestive heart failure
- Pulmonary infiltration with eosinophilia
- Large airway obstruction
- Pulmonary embolism
- Laryngeal dysfunction
When therapeutic goals are reached, medications should be decreased to the lowest amount needed to maintain wellbeing.

**Avoidance of stimuli**
- Remove animals and rugs, kill house dust mites, keep air warm and dry, avoid humidifiers and tobacco smoke. Methods to control dust mites include washing bed linens, blankets, and curtains weekly; avoiding use of carpets and fabric covered furniture; and maintaining humidity below 50%.
- Treat exacerbating conditions (for example, sinusitis and GERD).
- Consider radioallergosorbent technique (RAST) testing or referral to an allergist in refractory cases.

**Peak expiratory flow (PEF) monitoring**
- Consider peak flow monitoring once daily in the morning (pre- and post-bronchodilator) in patients with moderate to severe asthma.
- Monitoring is useful because patients often report subjective symptom resolution before objective improvement.
- The individual patient’s personal best peak flow should be used as the basis for a treatment plan.

**Medications**

**\( \beta_2 \) agonists**
- \( \beta_2 \) agonists given as needed are the treatment of choice for mild intermittent asthma.
- Intermediate acting agents (metaproterenol, albuterol, pirbuterol, terbutaline) usually have onset within five minutes, peak at approximately one hour and last approximately four hours.
- Longer acting agents (salmeterol inhaler and albuterol tablets) have a duration of action of approximately 8–10 hours.
- Supervised therapy with a \( \beta_2 \) agonist delivered by metered dose inhaler (MDI) with a spacer may be as effective as therapy with a nebulizer in hospitalized patients and in emergencies.
- Regular maintenance therapy with \( \beta_2 \) agonists (for example, albuterol 2 puffs qid) probably has no adverse effects, although many clinicians prefer prn schedules.
- Long acting \( \beta_2 \) agonists such as salmeterol taken bid on a regular schedule offer some clinical advantage to albuterol qid, even when the patient also takes a steroid inhaler.

**Steroid inhalers**
- Steroid inhalers are superior to \( \beta_2 \) agonist inhalers for chronic maintenance therapy.
- Inhaled beclomethasone has been shown to be highly effective for persistent asthma.

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3 A prospective study following children from birth to age 11 showed an association between house dust mite allergen exposure in infancy and active asthma later in childhood. The relative risk of asthma was 4.8 in children with high exposure. Sporik R, Holgate ST, Platts-Mills TA et al. Exposure to house dust mite allergen (der p I) and the development of asthma in childhood: a prospective study. N Engl J Med 1990;323:502–7.


A spacer device helps to decrease systemic levels of glucocorticoids. Approximately 90% is swallowed when a spacer is not used.

The most common side effects are dysphonia and candidiasis. When used in the suggested dose range, there are minimal effects on childhood growth, risk for tuberculosis, cataracts, exacerbation of diabetes, and pregnancy.

Calcium supplements or hormone replacement therapy should be considered to protect against osteoporosis in patients on chronic steroid therapy.

**Systemic steroids**

- Steroids offer a clinically important reduction in relapses in the first 7–10 days after emergent evaluation.
- There is no evidence that the route of administration (parenteral versus oral) affects admission rates or PFTs.
- Patients may not need a tapering of the steroid regimen if they have already received a 10 day course.
- Although very high dose regimens probably do little to improve the outcome after emergency evaluation, starting with <30 mg of prednisone per day is suboptimal.

**Theophylline**

- Has immunomodulatory and anti-inflammatory effects in addition to relatively weak bronchodilator activity.
- Somewhat less effective than steroid inhaler therapy for chronic maintenance, but provides clinical benefit when added to the regimen. Not useful for acute exacerbations.
- Levels should be 8–12 micrograms/ml, not near the standard upper limit of 20 micrograms/ml.
- Smokers may need higher doses.
- Evening doses taken between 8 and 10 pm may limit overnight declines in FEV₁.
- There are many significant drug interactions, especially with commonly prescribed antibiotics for COPD exacerbation (see Table 5.1).

**Mast cell stabilizers**

- Inhaled cromolyn sodium may be useful for prn prophylaxis and for chronic maintenance in place of steroid inhaler therapy.
- Beneficial when added to β₂ agonist inhalers and theophylline, but not when added to steroid inhaler therapy.
- Not as effective as steroids; used primarily in children.
- A trial of 4–6 weeks may be necessary to determine if cromolyn sodium will be of benefit.

**Leukotriene modifiers**

- Leukotrienes, produced by the 5-lipoxygenase pathway of arachidonic acid metabolism, may mediate bronchoconstriction and inflammation in asthmatic people.

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10 Tinkelman DG, Reed CE, Nelson HS et al. Aerosol beclomethasone dipropionate compared with theophylline as primary treatment of chronic, mild to moderately severe asthma in children. Pediatrics 1993;92: 64–77. Both were effective, but beclomethasone had fewer side effects and required less prn meds.


Table 5.1  Agents for asthma and COPD.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual dosage</th>
<th>Side effects and interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INHALERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β&lt;sub&gt;2&lt;/sub&gt; agonist inhalers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuterol (Proventil, Ventolin)</td>
<td>2 puffs q 4–6 h prn or 15 min before exercise</td>
<td>Tachycardia, rare supraventricular ectopy; ↓K&lt;sup&gt;+&lt;/sup&gt; at high doses</td>
</tr>
<tr>
<td></td>
<td>0.5% solution for home</td>
<td></td>
</tr>
<tr>
<td></td>
<td>nebulizer: 0.5 cc plus 2.5 cc saline by nebulizer tid-qid</td>
<td></td>
</tr>
<tr>
<td>Pirbuterol (Maxair)</td>
<td>2 puffs q 4–6 h prn</td>
<td></td>
</tr>
<tr>
<td>Metaproterenol (Alupent)</td>
<td>2 puffs q 3–4 h prn (max: 12 qd)</td>
<td>Metaproterenol: more β&lt;sub&gt;2&lt;/sub&gt; effect</td>
</tr>
<tr>
<td>Salmeterol (Serevent)</td>
<td>2 puffs bid</td>
<td>Salmeterol: not to be used prn</td>
</tr>
<tr>
<td><strong>Steroid inhalers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beclomethasone (Beclovent, Vanceril)</td>
<td>2–4 puffs bid-qid (max: 20 qd)</td>
<td>Dysphonia, oropharyngeal candidiasis</td>
</tr>
<tr>
<td>Budesonide (Pulmicort)</td>
<td>1–2 puffs bid (max: 4 bid)</td>
<td></td>
</tr>
<tr>
<td>Triamcinolone (Azmacort)</td>
<td>2–4 puffs bid (max: 8 qd)</td>
<td></td>
</tr>
<tr>
<td>Flunisolide (Aerobid)</td>
<td>1–3 puffs bid (max: 4 bid)</td>
<td></td>
</tr>
<tr>
<td>Fluticasone (Flovent 220)</td>
<td>1–2 puff bid (max: 4 bid)</td>
<td></td>
</tr>
<tr>
<td><strong>Anticholinergic inhalers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipratropium (Atrovent)</td>
<td>2 puffs qid</td>
<td>Cough, dry mouth, nausea, blurred vision. Use caution in patients with glaucoma and urinary retention</td>
</tr>
<tr>
<td>Ipratropium/albuterol (Combivent)</td>
<td>2 puffs qid</td>
<td></td>
</tr>
<tr>
<td>Mast cell stabilizer inhalers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cromolyn sodium (Intal)</td>
<td>2 puffs qid or before exercise</td>
<td>Cough, dry mouth</td>
</tr>
<tr>
<td><strong>ORAL MEDICATIONS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Steroids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone (Deltasone)</td>
<td>5–40 mg PO qd</td>
<td>Central obesity, facial puffiness, hyperglycemia, leukocytosis, etc.</td>
</tr>
<tr>
<td>Methylprednisolone (Medrol)</td>
<td>4–32 mg PO qd</td>
<td></td>
</tr>
<tr>
<td><strong>β&lt;sub&gt;2&lt;/sub&gt; Agonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuterol (Ventolin, Proventil)</td>
<td>2–4 mg PO tid prn or qHS prn</td>
<td></td>
</tr>
<tr>
<td>Terbutaline (Brethine)</td>
<td>2.5–5 mg PO tid</td>
<td></td>
</tr>
<tr>
<td><strong>Xanthine derivatives</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theophylline (Theo-Dur, Slo-Bid, Uniphyll)</td>
<td>150–300 mg PO bid or 200–300 mg PO qHS</td>
<td>Nausea, GE reflux, tachycardia, ventricular arrhythmia, seizures. Interactions: ↓[theo]: phenytoin, smoking ↑[theo]: β blockers, cimetidine, macrolides, quinolones</td>
</tr>
<tr>
<td><strong>Leukotriene modifiers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Montelukast (Singulair)</td>
<td>10 mg PO qd in the evening</td>
<td></td>
</tr>
<tr>
<td>Zafirlukast (Accolate)</td>
<td>20 mg PO bid, empty stomach</td>
<td></td>
</tr>
<tr>
<td>Zileuton (Zylo)</td>
<td>600 mg PO qid</td>
<td></td>
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</tbody>
</table>
In a randomized trial, zileuton, an inhibitor of 5-lipoxygenase, produced modest improvements in airflow in asthmatic patients, with minimal side effects.\textsuperscript{13} Montelukast, a leukotriene receptor antagonist, has shown modest protection against exercise induced bronchoconstriction.\textsuperscript{14} LT modifiers have not been compared to other treatments, only to placebo. They are well tolerated but expensive.

**Suggested stepwise approach for asthma based on symptoms**

1. **Mild intermittent asthma:** symptoms $\leq$ 2 times/week  
   - Albuterol inhaler prn  
   - Prophylactic albuterol or cromolyn sodium inhaler before exercise or exposure to an allergen  
   - No daily medications

2. **Mild persistent asthma:** symptoms 3–6 times/week but < daily  
   - Low dose steroid inhaler  
   - Albuterol inhaler prn  
   - Consider a leukotriene modifier or sustained release theophylline

3. **Moderate persistent asthma:** daily symptoms  
   - Medium dose steroid inhaler  
   - Long acting $\beta_2$ agonist inhaler bid  
   - Albuterol inhaler prn  
   - Consider sustained release theophylline

4. **Severe persistent asthma:** continuous symptoms limiting activity  
   - High dose steroid inhaler  
   - Long acting $\beta_2$ agonist inhaler bid  
   - Oral steroids  
   - Albuterol inhaler prn

Consider an oral steroid taper in all patients with acute attacks, even if the attack is relatively mild. Oral steroids may be discontinued when the patient is able to do 80% of optimal peak flow.

For patients with predominantly nocturnal symptoms, use PM theophylline, a long acting $\beta_2$ agonist, or a steroid inhaler.

For exercise induced asthma, use a $\beta_2$ agonist prior to exercise. Cromolyn sodium is the second choice.

For patients without a history of asthma who present with symptoms of “bronchitis with bronchospasm” or “asthmatic bronchitis,” consider a short course of steroids (prednisone 30mg PO qd for three days if symptoms are not severe), in addition to $\beta_2$ agonists.

For acute exacerbations which do not require hospitalization, the prompt use of oral steroids and increased $\beta_2$ agonist inhaler therapy is indicated.

\textsuperscript{13} Liu MC, Dube LM, Lancaster J. Acute and chronic effects of a 5-lipoxygenase inhibitor in asthma: a 6 month randomized multicenter trial. J All Clin Immun 1996;98:859–71. This trial included 373 patients with mild to moderate asthma. The 600mg dose of zileuton increased FEV\textsubscript{1} by 10% and morning PEF by 7–10% over placebo.

\textsuperscript{14} Leff JA, Busse WW, Perlman D et al. Montelukast, a leukotriene-receptor antagonist, for the treatment of mild asthma and exercise-induced bronchoconstriction. N Engl J Med 1998;339:147–52. Montelukast reduced the exercise-induced decrease in FEV\textsubscript{1} by about 8 percentage points.

**Additional features of asthma severity**

- **Mild intermittent:** brief exacerbations (hours to a few days), night-time symptoms < 2/month, asymptomatic between exacerbations, FEV\textsubscript{1} > 80% predicted
- **Mild persistent:** exacerbations may affect activity and sleep, night-time symptoms occur > 2/month, FEV\textsubscript{1} > 80% predicted
- **Moderate persistent:** exacerbations affect activity and sleep, night-time symptoms occur > 1/week, daily use of albuterol inhaler is reported, FEV\textsubscript{1} is 60–80% predicted
- **Severe persistent:** frequent exacerbations, frequent night-time symptoms, FEV\textsubscript{1} < 60% predicted

**Technique for inhaler use**

1. Shake canister.
2. Hold mouthpiece 4cm in front of open mouth or use spacer.
3. Breathe out completely.
4. Discharge inhaler while inhaling slowly (5 seconds) and deeply.
5. Hold breath (10 seconds), then exhale slowly.
6. Repeat steps after one minute.
### Table 5.2  Predicted average peak expiratory flow (l/min) for normal men.

<table>
<thead>
<tr>
<th>Age</th>
<th>Height in inches</th>
<th>60</th>
<th>65</th>
<th>70</th>
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<tbody>
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<td>564</td>
<td>603</td>
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<td>70</td>
<td></td>
<td>440</td>
<td>477</td>
<td>515</td>
<td>550</td>
<td>587</td>
</tr>
</tbody>
</table>


**Occupational asthma**<sup>15</sup>

- Approximately 15% of new adult cases of asthma are due to occupational exposure.
- The most common type is occupational asthma with latency. Periods of exposure may vary from a few weeks to a few years before the onset of symptoms.
- Occupational asthma without latency follows exposure to high concentrations of irritant gases (for example, chlorine and ammonia).
- Diagnosis often requires evaluation by a subspecialist trained in occupational health in order to differentiate occupational from non-occupational asthma and to determine the cause.
- The majority of patients (60–90%) fail to recover even several years after leaving the exposure and are often permanently disabled.<sup>16</sup>
- Early diagnosis and cessation of exposure increase the likelihood of a favorable outcome. Job modification, such as improved ventilation, is rarely warranted.

**Chronic obstructive pulmonary disease (COPD)**

**Epidemiology**

- In 1996, over 14 million cases of chronic bronchitis and 1 million cases of emphysema were reported in the US.<sup>2</sup>
- In 1998, COPD caused 112,584 deaths – the fourth leading cause of death in the US.
- Emphysema rates are highest for males aged 65 and over.


• Approximately 15% of smokers will develop COPD.\textsuperscript{17}
• Of patients with COPD, 10% have a cause other than smoking.
• Most patients with COPD have one exacerbation per year, 15% have none, and 10% have 3–4 exacerbations per year.
• Lung cancer incidence is higher in patients with chronic airway obstruction than in controls matched for age, sex, and smoking.

## Diagnosis

• A spectrum of respiratory disease characterized by cough, sputum, dyspnea, airflow limitation, and impaired gas exchange.
• Patients with COPD often have a combination of the following two clinical pictures.

1. \textit{Chronic bronchitis} is defined by the presence of cough and sputum on most days for >3 months for >2 years. These patients tend to have more hypoxemia, hypercarbia, and erythrocytosis than patients with emphysema.
2. \textit{Emphysema} is defined as permanent enlargement of distal airspaces without evidence of fibrosis. These patients have a greater reduction in the diffusing capacity of carbon monoxide (DL\textsubscript{CO}) than patients with chronic bronchitis.

• COPD is characterized by irreversible airflow limitation; in asthma, airway obstruction is reversible. There is overlap between asthma, chronic bronchitis, and emphysema that is difficult to quantify.

\textbf{Table 5.3  Predicted average peak expiratory flow (l/min) for normal women.}

<table>
<thead>
<tr>
<th>Age</th>
<th>55</th>
<th>60</th>
<th>65</th>
<th>70</th>
<th>75</th>
</tr>
</thead>
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<td>496</td>
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<td>25</td>
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<td>490</td>
<td>523</td>
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<tr>
<td>30</td>
<td>380</td>
<td>413</td>
<td>448</td>
<td>483</td>
<td>516</td>
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<tr>
<td>35</td>
<td>375</td>
<td>408</td>
<td>442</td>
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<td>509</td>
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<td>70</td>
<td>340</td>
<td>369</td>
<td>400</td>
<td>432</td>
<td>461</td>
</tr>
</tbody>
</table>


\textsuperscript{17} American Thoracic Society (ATS) recommendations. Standards for the diagnosis and care of patients with COPD. Am J Respir Crit Care Med 1995;152:S78–S121.
Bronchitis is rarely diagnosed by chest radiograph alone. Chest radiographs are used mainly to exclude other diagnoses.

The presence of bullae, hyperinflation, and paucity of peripheral arteries is virtually diagnostic of emphysema.

Features suggestive of α₁ antitrypsin deficiency in patients with emphysema include onset at 30–50 years, emphysema in a non-smoker, basilar predominance, liver disease, and a family history of COPD before age 50.

**Indications for Pulmonary Function Testing**

- Diagnostic: to evaluate symptoms (cough, dyspnea, wheezing) and signs (overinflation, abnormal radiographs).
- Monitoring: to assess the response to β agonists, effectiveness of therapy, or a specific pulmonary disease when adequate baseline studies are available.
- Evaluative: preoperative, disability, rehab evaluations.

**Interpretation of PFTs**

- The primary guides are forced vital capacity (FVC), forced expiratory volume in 1 second (FEV₁), and FEV₁/FVC.
- The best indicator of obstruction is a reduced FEV₁/FVC (normal: >60% in men, >70% in women). However, the best measure of severity is the FEV₁. Although the FEV₂₅₋₇₅% in obstructive disease may decline more than the FEV₁/FVC, it is not very useful in assessing severity.
  - Patients with moderate obstruction but with FEV₁ > 1l have only a slightly increased mortality at 10 years.
  - Patients with FEV₁ < 0.75l have a mortality rate of 30% at one year and a mortality rate of 95% at 10 years.

- ATS staging: Stage I: FEV₁ > 50% predicted
  - Stage II: FEV₁ 35–49% predicted
  - Stage III: FEV₁ < 35% predicted

- A positive response to bronchodilators is defined as a 12% change in the FEV₁ and an absolute improvement of 200cc after treatment with a β₂ agonist inhaler.

- Changes from baseline values are more meaningful than comparison with population standards.

**Treatment**

- *Smoking cessation* is the only intervention found to slow the progression of COPD. In one study the smoking cessation group had smaller declines in FEV₁ at five years.

- *Bronchodilators* (ipratropium, β₂ agonists, and theophylline) are the mainstays of the pharmacological treatment of COPD.

- *Corticosteroids* are useful for patients hospitalized for COPD exacerbations. Their effectiveness in long term outpatient management is controversial.

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The sensitivity of pulmonary function testing in the diagnosis of COPD is only 5–15% in young, minimally symptomatic smokers (specificity ~90%). Sensitivity increases to only 20–50% in moderately symptomatic or >20 pack-year smokers. Thus, PFT’s are not very useful in asymptomatic patients with minimal smoking histories who wish to know the extent of their lung disease from smoking. Martin R. The early detection of airway obstruction. Am Rev Respir Dis 1975;111:119–25.

A patient may respond to long term bronchodilation even if reversibility is not seen in a single PFT session. The definitive finding for a restrictive pattern is a reduced total lung capacity (TLC), though one may infer restriction when the vital capacity (VC) is reduced and FEV₁/FVC is normal or increased.


20 Anthonisen NR, Connell JE, Kiley JP et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV₁. The Lung Health Study. JAMA 1994;272:1497–505. 5887 smokers with early COPD were randomized to smoking cessation, smoking cessation plus ipratropium 2 puffs tid, or no intervention. Ipratropium caused a small improvement in FEV₁ that disappeared when the drug was stopped; it did not slow the long term progression of disease.
Ipratropium
- A 1996 review of randomized trials found long term therapy with ipratropium to be effective, and superior to long term therapy with \( \beta_2 \) agonists for COPD.\(^{21}\)

\( \beta_2 \) Agonists
- A 1999 trial reached the opposite conclusion. The long acting \( \beta_2 \) agonist salmeterol 2 puffs bid was superior to ipratropium 2 puffs qid in improving lung function.\(^{22}\)
- Inhaled albuterol as needed is effective for symptom control.
- A combination of albuterol and ipratropium in a metered dose inhaler is marketed as Combivent.

Theophylline
- Theophylline was found to be beneficial as a third agent when added to ipratropium and albuterol.\(^{23}\)

Corticosteroids
- Steroids do not suppress the neutrophil predominant inflammation of COPD as well as they suppress the eosinophil predominant inflammation of asthma. In trials of steroids for COPD, the inclusion of patients who have an element of asthma is a confounding factor that makes steroids appear more beneficial than they are in pure COPD.
- Long term high dose steroid therapy does not slow the long term decline in \( \text{FEV}_1 \) in COPD.\(^{24,25}\)
- Steroids have caused moderate improvement in patients hospitalized for acute COPD exacerbations.\(^{26}\)

Antibiotics
- In COPD exacerbations, antibiotics have shown a small improvement in \( \text{FEV}_1 \) that may be clinically important in patients with severe disease.\(^{27}\)
- There is no role for long courses of prophylactic antibiotics.

Home oxygen
- Long term oxygen therapy has been shown to improve mortality in patients with arterial \( \text{PaO}_2 <60 \text{mmHg} \), but not in patients with only moderate hypoxemia or nocturnal oxygen desaturation.\(^{28}\)
- Indications for continuous therapy with home oxygen:
  - \( \text{PaO}_2 <55 \text{mmHg} \) or \( \text{O}_2 \) saturation <89% at rest
  - \( \text{PaO}_2 56–59 \text{mmHg} \) or \( \text{O}_2 \) saturation \( \leq 89\% \) with evidence of pulmonary hypertension, cor pulmonale, or polycythemia.
- Benefits are more notable when \( \text{O}_2 \) is used >18 hours per day.
- Airline travel is safe for most patients; patients should increase flow by 1–2 l during the flight.

\(^{21}\) Rennard SI, Serby CW, Ghafouri M, Johnson PA, Friedman M. Extended therapy with ipratropium is associated with improved lung function in chronic obstructive pulmonary disease: a retrospective analysis of data from seven clinical trials. Chest 1996;110:62–70. Long term therapy with ipratropium resulted in a 28 ml improvement in \( \text{FEV}_1 \) and a 131 ml improvement in \( \text{FVC} \). Long term therapy with \( \beta_2 \) agonists caused no significant improvement.


\(^{24}\) Vestbo J, Sorenson T, Lange P, Brix A, Torre P, Viskum K. Long term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. Lancet 1999;353:1819–23. At three years, inhaled budesonide showed no benefit in the rate of \( \text{FEV}_1 \) decline over placebo.

\(^{25}\) Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. BMJ 2000;320: 1297–303. Patients taking 500 micrograms twice a day did have fewer exacerbations and slower decline in overall health status.


Possible stepwise strategy for COPD treatment
1. Salmeterol 2 puffs bid
2. Ipratropium 2–4 puffs tid-qid or as needed
3. Theophylline
4. Steroid inhaler
   • During exacerbations, empiric antibiotics against Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis.
   • Steroids during exacerbations
   • Pneumococcal vaccine
   • Influenza vaccine every year

Indications for subspecialty referral
• Life threatening exacerbation
• Difficult differential diagnosis
• Entities that complicate airway disease (sinusitis, nasal polyps, aspergillosis)
• Additional diagnostic testing: bronchoscopy, allergy testing
• Stage II and III disease (see text under pulmonary function tests).

Antibiotics improved peak flow by ~ 101/min compared to placebo in this analysis of nine trials.

6 Atrial fibrillation
Michael LoCurcio

Epidemiology

Prevalence
- The lifetime risk of atrial fibrillation (AF) is about 2%. The 22 year cumulative incidence for AF in the Framingham cohort was 2.2 per 100 men and 1.7 per 100 women.¹
- Prevalence greatly increases with age. AF affects 0.5% of people aged 50–59 and 9% of people aged 80–89.¹
- The many other risk factors include heart failure, valvular disease, hypertension, diabetes, coronary artery disease (CAD), myocarditis, cardiomyopathy, Wolf–Parkinson–White syndrome, pericarditis, surgery, fever, thyrotoxicosis, alcoholism, infection, pulmonary embolism, lung cancer, and other lung disease.

Morbidity and mortality
- Total mortality from all cardiovascular disease in the presence of AF is almost twice as high as that in matched controls without AF.²
- In a multivariate analysis, subjects with AF were five times as likely to have stroke as matched controls without AF.¹
- One out of six strokes occurs in a patient with AF.
- About 10% of ischemic strokes are thought to originate from left atrial thrombi.³

Diagnosis

History
- Most patients are asymptomatic at the time of diagnosis.
- AF may be paroxysmal or chronic.
- Many patients present initially with symptoms of a transient ischemic attack (TIA) or stroke (see Chapter 9).
- Possible precipitants: acute alcohol or drug use, hyperthyroidism, infection, pulmonary embolism, coronary ischemia, valvular heart disease, hypertensive crisis, heart failure.
- When symptoms of AF are present they may include palpitations, dyspnea on exertion, decreased exercise tolerance, and chest pain.¹

Physical examination
- A thorough exam should include blood pressure, heart rate, respiratory rate, examination for thyroid and valvular abnormalities, and for signs of heart failure and infection.
- Classically, patients with AF exhibit an irregularly irregular heart rhythm and lack a jugular venous A-wave.

Diagnostic tests
- An ECG is essential to verify the diagnosis and to check for an accessory AV pathway, as in the Wolf–Parkinson–White syndrome.

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Other tests that may be useful include thyroid function tests, chest radiograph, and transthoracic and transesophageal echocardiography (see therapy).

**Therapy**

Beyond the treatment of acute precipitants, therapeutic issues in the treatment of AF involve rate control, stroke prevention, cardioversion, maintenance of sinus rhythm, and ablation therapy. Patients who are hemodynamically unstable require immediate electrical cardioversion.

**Ventricular rate control**

While it is common practice to control the ventricular rate in AF, the benefits of rate control have not been thoroughly studied in a prospective randomized manner. Presumed benefits of rate control include:

- adequate filling time to avoid heart failure, coronary ischemia, and hypoperfusion
- relief of palpitations
- decreased oxygen consumption (many patients have occult coronary artery disease)
- less risk of rate related cardiomyopathy.

**Cardiac glycosides**

- Digitalis is the classic agent for rate control in atrial fibrillation.4,5
- Small studies have confirmed that digoxin is effective in controlling the resting heart rate, presumably by increasing vagal tone at the AV node. Much of this slowing effect is negated by exercise.4,5

**β Blockers**

- β blockers are effective at regulating rate and, unlike digoxin, provide some benefit during exercise.4 Most studies of β blockers have excluded patients with pulmonary disease, although many of these patients have coronary artery disease and would likely benefit from β blockers.
- β blockers may be the best initial agent for rate control, given the high association of AF and CAD.

**Calcium channel blockers**

- Both verapamil and diltiazem5 are effective in the control of ventricular rate in AF and seem to be superior to digoxin.
- Like β blockers, calcium channel blockers maintain some efficacy during exercise.5

**Combination therapy**

- Digoxin may be beneficial as a second agent for rate control with either diltiazem or β blockers.4,5

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4 David D, Segnio E, Klein H, Kaplinsky E. Inefficacy of digitalis in the control of heart rate in patients with chronic atrial fibrillation: beneficial effect of an added beta adrenergic blocking agent. Am J Cardiol 1979;44:1378–82. 28 patients were treated with digoxin or timolol. Mean heart rate at rest and exercise was 95 and 137 for digoxin v 67 and 92 for timolol.

5 Roth A, Harrison E, Mitani G, Cohen J, Rahimtoola S, Elkayam U. Efficacy and safety of medium and high dose diltiazem alone and in combination with digoxin for control of heart rate at rest and during exercise in patients with chronic atrial fibrillation. Circulation 1986;73:316–24. 12 patients with chronic AF were treated with digoxin and/or diltiazem.

<table>
<thead>
<tr>
<th></th>
<th>HR (rest)</th>
<th>HR (exercise)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td>86</td>
<td>170</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>79</td>
<td>136</td>
</tr>
<tr>
<td>Both</td>
<td>65</td>
<td>121</td>
</tr>
</tbody>
</table>

Continued
• Combined β blocker and calcium antagonist therapy is often needed for rate control in chronic AF. Excessive suppression of sinus node function is a risk in patients with paroxysmal AF who depend upon adequate sinus function when not in AF.
• β blockers and calcium antagonists should be used cautiously in patients with impaired left ventricular function.

Paroxysmal atrial fibrillation
• There have been few studies of rate control for patients with paroxysmal AF during actual episodes.
• Despite the lack of data, it remains common practice to treat patients with β blockers and calcium channel blockers in an attempt to control rate, particularly in patients with frequent symptomatic episodes.

Wolf–Parkinson–White syndrome and rate control
• Digoxin and calcium channel blockers have been implicated in increasing the rate of ventricular response in patients with accessory conduction pathways. This appears to be due to a decrease in refractoriness of the accessory pathways.
• It is important, therefore, to rule out the possibility of an accessory pathway (i.e., assess ECG for wide QRS complexes with δ waves) before administering these agents.

Stroke prevention
Atrial fibrillation has clearly been implicated as a cause of stroke, but the actual risk of stroke varies among patients with AF. Three distinct populations (non-valvular AF, valvular AF, and lone AF) have been defined in the literature and been studied to different degrees.

Non-valvular atrial fibrillation
• This is by far the largest, most heterogeneous, and most extensively studied group of patients with AF. Population analyses have identified the risk factors for stroke: age, hypertension, previous stroke or TIA, diabetes, and female sex.
• The strongest predictor of stroke is age.
• Several randomized trials have definitively demonstrated that anticoagulation with warfarin decreases the risk of stroke in this population. (See Table 6.2 for a summary of the trials.)
• On average, 3–5 strokes were prevented each year for every 100 patients anticoagulated with warfarin (RRR = 68%, ARR = 4%).
• Of the patients in the warfarin groups who did experience stroke, many were either not taking the medication or had an INR which was lower than the study design.
• Aspirin is not as effective as warfarin. In the trials that included aspirin, the average relative risk reduction was 18%.
• In most studies, the risk of significant bleeding (leading to death, transfusion or hospital admission) was not different among those taking aspirin, warfarin at INR 2–3, and
placebo. Bleeding did increase at higher INR levels and in the elderly. The rate of minor bleeding was greater among those taking warfarin.

- There may be a subgroup of patients with non-valvular AF who do not benefit from warfarin. The SPAF III trial identified higher risk of stroke in patients with hypertension, prior thromboembolism, heart failure or who were women over the age of 75. Patients without these criteria had a rate of stroke less than 2% while on aspirin.

**Valvular atrial fibrillation**

- Most patients in this group have rheumatic heart disease, which is still a major health problem in developing countries. The risk of stroke is higher than that of patients with non-valvular AF.
- These patients were excluded from most of the large trials done on anticoagulation for stroke prevention.
- There have been no large prospective studies of this group. Most experts anticoagulate these patients with warfarin, as in non-valvular AF.

### Table 6.1 Drugs for atrial fibrillation.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual dose</th>
<th>Special parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticoagulants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin (Coumadin)</td>
<td>1–10 mg PO qHS</td>
<td>INR maintained between 2 and 3</td>
</tr>
<tr>
<td><strong>Antiplatelet agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>81–325 mg PO qd</td>
<td></td>
</tr>
<tr>
<td><strong>Agents for rate control</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>0.125–0.5 mg qd</td>
<td>Periodic digoxin levels. Monitor for symptoms and signs of toxicity. Digoxin is cleared renally. Levels are affected by other medications. Rule out WPW prior to use</td>
</tr>
<tr>
<td><strong>β blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atenolol (Tenormin)</td>
<td>25–100 mg PO qd</td>
<td>Monitor heart rate and symptoms of worsening heart failure or COPD</td>
</tr>
<tr>
<td>Propranolol (Inderal) (Inderal LA)</td>
<td>20–320 mg PO bid 80–640 mg PO qd</td>
<td></td>
</tr>
<tr>
<td>Metoprolol (Lopressor) (Lopressor ER)</td>
<td>25–225 mg PO bid 25–400 mg PO qd-bid</td>
<td></td>
</tr>
<tr>
<td><strong>Calcium channel blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diltiazem (Cardizem) (Tiaz)</td>
<td>30–60 mg PO qid 120–540 mg PO qd</td>
<td>Monitor heart rate and symptoms of CHF. Rule out WPW prior to use for rate control</td>
</tr>
<tr>
<td>Verapamil (Calan) (Calan SR)</td>
<td>40–80 mg PO tid-qid 120–480 mg PO qd-bid</td>
<td></td>
</tr>
</tbody>
</table>

### Footnotes:


Lone atrial fibrillation

- This group comprises only about 3% of patients with atrial fibrillation and represents those with non-valvular AF and no other risk factors for thromboembolism.
- The definition of lone AF varies from study to study and probably explains the difference in outcomes.  

Some authors advocate the use of aspirin in patients with lone AF, but this has not been independently studied. Others avoid the term “lone AF” and treat patients based on risk factors.

American College of Chest Physicians recommendations

- The American College of Chest Physicians describes definite and probable risk factors for stroke.
  - Definite risk factors: previous TIA, stroke, or thromboembolic event; hypertension; heart failure; age > 75
  - Probable risk factors: mitral stenosis, prosthetic valves, diabetes, coronary artery disease, age 65–75, thyrotoxicosis
- They recommend that the following patients with chronic or paroxysmal AF receive warfarin at INR 2.0–3.0.
  - All patients with definite risk factors or mitral stenosis or prosthetic valves
  - All patients > 75 years
  - Patients < 65 years without risk factors can potentially be given aspirin
  - For patients aged 65–75 years or those with probable risk factors, it is an individual decision, weighing risks, benefits, and patient preference.

Cardioversion

- Although there have been few studies proving the benefit of cardioversion, there is a general consensus that it should be attempted in symptomatic patients in whom success is likely. The larger the atrial size and the longer the duration of AF, the lower the chance that cardioversion will be successful or that sinus rhythm will be maintained.
- Cardioversion carries a risk of thromboembolic events and, with a few exceptions, most experts recommend anticoagulation.
- The American College of Chest Physicians recommends anticoagulation with warfarin (INR 2–3) for three weeks before cardioversion and four weeks after.
- Some studies have suggested that it is safe to forego anticoagulation if transesophageal echocardiography shows no atrial thrombus prior to cardioversion. However, these patients must still be anticoagulated for one month following cardioversion.
- Patients with AF who are hemodynamically unstable should have immediate electrical cardioversion.


13 Brand F, Abbott R, Kannel W, Wolf P. Characteristics and prognosis of lone atrial fibrillation. JAMA 1985;254:3449–53. In this case-control analysis of Framingham data, the risk of thromboembolism was four times higher than control. The definition of lone AF excluded patients with CAD, heart failure, rheumatic heart disease, or hypertensive heart disease.

14 Kopecky S, Geis B, McGoon M et al. The natural history of lone atrial fibrillation: a population based study over three decades. N Engl J Med 1987;317:669–74. In this cohort study, the risk of stroke was no different than control. The definition of lone AF excluded all patients with age over 60, hypertension, diabetes, heart failure, COPD, hyperthyroidism, valvular disease (including mitral valve prolapse), CAD, cardiomyopathy, and cardiomegaly on chest radiograph.


17 Manning W, Silverman D, Gordon S, Krumholz H, Douglas P. Cardioversion from atrial fibrillation without prolonged anticoagulation with use of transesophageal echocardiography to exclude the presence of atrial thrombi. N Engl J Med 1993;328:750–5. 96 patients with AF underwent TEE. In the 82 without atrial thrombus, immediate cardioversion was successful in 79. There were no embolic phenomena. Most patients were anticoagulated for one month afterward.
Electrical cardioversion
- Direct current cardioversion remains the most effective and rapid method and is initially effective in about 80% of cases.\(^\text{16}\) It is the method of choice in the setting of hemodynamic instability.
- The adverse effects of electrical cardioversion include pain, thromboembolism, and rare cases of ventricular fibrillation.

Chemical cardioversion
- Class IA, IC, and III antiarrhythmics have been shown to be effective in converting AF to sinus rhythm; however, long term safety concerns have limited their use in maintaining sinus rhythm. These agents should be administered in consultation with a cardiologist in an inpatient setting.
- In most studies of chemical cardioversion, patients were included only if they had been in AF for a short period of time. Patients with significant conduction abnormalities were excluded.
- Digoxin, calcium channel blockers, and β blockers have not been proven to be more effective than placebo in converting patients with AF to sinus rhythm.\(^\text{18}\)

Maintenance of sinus rhythm after cardioversion
- While it is relatively simple to convert AF to sinus rhythm by electrical or chemical means, it is often difficult to maintain sinus rhythm. In addition, antiarrhythmics have many side effects that complicate long term use. All antiarrhythmics can be proarrhythmic.
- Class IA agents (quinidine and disopyramide) can decrease the refractoriness of the AV node and are therefore usually used in conjunction with a rate control agent. Some studies have shown increased mortality with quinidine.\(^\text{19}\)
- Class IC agents (flecainide and propafenone) have also been shown to be effective for maintenance of sinus rhythm and comparable to class IA agents. These agents do not require the use of a second agent for rate control. Associated ventricular arrhythmias can be life threatening.\(^\text{20}\)
- Amiodarone has been shown to be more effective and better tolerated than quinidine in the maintenance of sinus rhythm.\(^\text{21}\)
- Amiodarone has many extracardiac toxicities including pulmonary fibrosis, hyper- and hypothyroidism, hepatotoxicity, peripheral neuropathy, skin discoloration, photosensitivity, tremor, and nausea. Many of these effects are dose related and occur less frequently with doses < 300 mg per day.\(^\text{21}\)

Ablation therapy
- Ablation therapy is usually indicated in those with an accessory pathway and rapid AF.

Synchronized DC cardioversion is carried out on sedated inpatients in a monitored setting. In unstable patients, there may not be time to set up synchronization and give sedation. Also, sedatives may lower the blood pressure in an already unstable patient.
Side effects include AV block, pericarditis, and cardiac tamponade. These have been reported in less than 2% of patients.\textsuperscript{22,23}

Catheter ablation of the AV node with pacemaker placement has been shown to be effective and beneficial to patients refractory to medical therapy.\textsuperscript{24}

New ablative procedures are in development (for example, pulmonary vein ablation to eliminate the triggering focus).

### Table 6.2 Selected studies of warfarin in the prevention of thromboembolic events in patients with non-valvular AF.

<table>
<thead>
<tr>
<th>Design</th>
<th>N</th>
<th>RRR (%)</th>
<th>ARR (%)</th>
<th>P</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin v placebo for primary prevention of an embolic event. Separate arm to test aspirin. Target INR 2.0–4.5</td>
<td>1330</td>
<td>67</td>
<td>5.1</td>
<td>0.01</td>
<td>Stroke Prevention in Atrial Fibrillation Investigators. Stroke prevention in atrial fibrillation. Circulation 1991;84:527–39. (SPAF)</td>
</tr>
</tbody>
</table>

\textsuperscript{22} Heinz G, Siostrzonek P, Kreiner G, Gossinger H. Improvement in left ventricular systolic function after successful radiofrequency His bundle ablation for drug refractory, chronic atrial fibrillation, and recurrent atrial flutter. Am J Cardiol 1992;69:489–92. 91% of subjects remained free of accessory pathways at eight months.


Table 6.2  Continued

<table>
<thead>
<tr>
<th>Design</th>
<th>N</th>
<th>RRR (%)</th>
<th>ARR (%)</th>
<th>P</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin v placebo for secondary prevention of all stroke. Aspirin was studied in a separate arm. Target INR 2.4–4.0</td>
<td>669</td>
<td>48</td>
<td>8</td>
<td>0.04</td>
<td>European Atrial Fibrillation Trial Study Group. Secondary prevention in nonrheumatic atrial fibrillation after transient ischemic attack or minor stroke. Lancet 1993;342:1255–62. (EAFT)</td>
</tr>
</tbody>
</table>
7 Breast disease
Susan Urban

Introduction
- Female patients frequently present to their primary care physicians with breast symptoms.
- One recent retrospective cohort study\(^1\) of 2400 women aged 40–69 enrolled in a large HMO found that over a 10-year period 16% of this group presented with breast symptoms, including breast mass, asymmetric thickening, pain, nipple discharge and skin changes. 71% of the visits were to internists.
- While most breast complaints have a benign etiology, a significant minority lead to a diagnosis of breast cancer. In the study above, breast cancer was found in 6.2% of patients. Having any symptom was associated with a likelihood ratio of 24 for breast cancer.
- One role of the primary care physician is to evaluate breast complaints and facilitate the diagnostic process with the ultimate goal of determining whether the patient has breast cancer.

Evaluation of a breast mass\(^2\)

History
- Time course: when the mass was first noted; subsequent changes in size, consistency, and mobility
- Other symptoms: skin changes, nipple discharge or erosion, axillary or supraclavicular lymph nodes, breast pain, and symptoms potentially related to metastatic disease such as bone pain, dyspnea, mental status changes
- Results of any previous imaging studies or biopsies
- Risk factors for breast cancer: see below

Physical examination
- The goal is to determine whether the patient has a dominant breast mass and to perform a complete examination looking for possible metastatic disease.
- Breast examination: inspect and palpate the breasts with the patient in sitting and supine positions. Also assess for nipple discharge and skin changes.
- Examine axillary and supraclavicular areas for nodes.
- Physical examination leads to correct identification of malignancy in 60–85% of cases.\(^3\)
- Not all breast cancers are hard, with irregular borders, and fixed. Sensitivities of specific physical findings for malignancy were the following in one study:\(^4\)
  - not soft or cystic 62%
  - irregular borders 60%
  - not freely movable 40%

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1. Barton B, Elmore JG, Fletcher SW. Breast symptoms among women enrolled in a health maintenance organization: frequency, evaluation, and outcome. Ann Intern Med 1999;130:651–7. Barton et al. found the following:

| Rate of breast symptom episodes over all age ranges |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Mass            | Lumpiness       | Pain            | Nipple discharge/skin change | Other |
| 42%             | 8%              | 47%             | 14%                         | 1%    |


The differential diagnosis of a dominant breast mass includes fibrocystic change, cyst, fibroadenoma, fat necrosis, and breast carcinoma. Overall about 80% of all breast masses are benign.

The best time to examine a premenopausal women is 7–9 days after the onset of the menses. A premenopausal woman can be re-examined after her menses if an abnormality is found just prior to menses.

A good description of the clinical breast exam is in the following article:


Image studies

Mammography

- Diagnostic mammography should be the first imaging study in women 35 and older with a breast mass.
- The Breast Image Reporting and Data System developed by the American College of Radiology\(^5\)\(^6\) categorizes results as:
  - BI-RADS 1: negative
  - BI-RADS 2: benign
  - BI-RADS 3: probably benign
  - BI-RADS 4: suspicious
  - BI-RADS 5: highly suggestive of malignancy
- The accuracy of mammography is lower in women with dense breast tissue, as is found in premenopausal women\(^7\).
- Mammography can be negative in 15–25% of breast cancers.
- If there is a persistent mass on physical exam and the mammogram is negative, it is important to obtain a tissue diagnosis unless other studies show unequivocally that the mass is benign.
- Mammography should be done before biopsy of a breast mass in order to characterize the mass and to look for other lesions. In addition, mammography should be done before biopsy since a biopsy can change the breast appearance on the mammogram.

Ultrasound of the breast

- Ultrasound should be the first imaging study in women under 35 with a breast mass.
- Pregnant women should undergo ultrasonography for evaluation of a breast mass. Pregnant women with known breast cancer or a lesion very suspicious for breast cancer should also undergo mammography.
- Ultrasound can distinguish cystic from solid masses.
- Newer ultrasound techniques, such as image texture analysis and Doppler flow analysis, can help distinguish benign from malignant solid lesions.

Tissue diagnosis

Fine needle aspirate (FNA)

- Obtains material with a 22 gauge needle which can then be sent for cytology.
- Distinguishes cystic from solid lesions.
- Can provide both diagnosis and treatment for a cyst.
- Can be used to aspirate a solid mass for cells. However, the small sample size limits the efficacy of FNA in diagnosing solid lesions. Insufficient material may lead to false negative results. FNA provides no information on the architecture and therefore cannot give information about invasion.

"Triple test."\(^8\)

- Some suggest that the combination of FNA, mammography, and physical examination can effectively guide management of breast masses in young, low risk populations.

\(^5\) American College of Radiology: Breast Imaging Reporting and Data System, ed Reston, VA, American College of Radiology, 1995. Suggested follow up of category 3 is mammogram of the affected breast in 6 months followed by mammogram of both breasts at 1, 2, and 3 years. Suggested follow up for category 4 and 5 is biopsy.

\(^6\) Approximately 33% of category 4 lesions and 90% of category 5 lesions are found to be malignant on biopsy. Liberman L. Breast imaging: clinical management issues in percutaneous core breast biopsy. Radiol Clin North Am 2000;38:791–807.


Newer imaging techniques are being developed, including digital mammography, MR imaging, nuclear imaging with technetium sestamibi, and positron emission imaging. Potential uses of these techniques include imaging women with breast implants, women with dense breasts and equivocal mammogram results, and women previously treated with lumpectomy and radiation looking for recurrent disease.


If all three are negative for malignancy, the likelihood of cancer has been estimated to be less than 1%.

Morris has proposed the triple test score, in which 3 points are assigned to the FNA, mammogram, and physical examination. In one study, he found that masses that scored 4 or lower were benign, masses that scored 6 or higher were malignant, and masses that scored 5 points needed open biopsy for evaluation.9

### Core needle biopsy (CNB)
- A 14 gauge needle obtains more tissue than FNA and therefore is more often diagnostic of a solid mass.
- It allows a histologic diagnosis and gives information about invasion.
- Excisional biopsy should be done when the CNB is non-diagnostic or when the CNB shows atypical ductal hyperplasia or DCIS or when calcifications are not removed on CNB.

### Open biopsy
- Excisional biopsy: complete excision of the mass
- The gold standard for diagnosis of solid masses
- Should be done when FNA and/or CNB cannot give an adequate diagnosis.

### Evaluation of abnormal mammograms when the breast exam is normal

#### Criteria for biopsy
- Localized soft tissue density which is new, changed from prior mammogram, or suspicious for cancer
- Microcalcifications which are not clearly benign

#### Methods of biopsy
- Core needle biopsy with stereotactic localization
- Excisional biopsy with wire localization

### Mastalgia
- Up to 70% of women report some breast pain. About 8–10% of women report moderate or severe pain.
- Breast cancer presents rarely as breast pain. Up to 10% of breast cancer has been associated with breast pain in some studies. However, often the breast pain was associated with a mass.
- Breast pain may or may not vary with the menstrual cycle. Cyclic pain increases prior to menses and can be associated with fibrocystic change. Cyclic pain is more common than non-cyclic pain and responds better to treatment.
- Non-cyclic breast pain does not fluctuate with the menstrual cycle. The differential diagnosis includes hematoma, fat necrosis, ruptured cyst, infection, and breast cancer. Rarely, pulmonary, cardiac, and musculoskeletal disease can be responsible for the pain.

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• Evaluation: history, physical examination, mammogram in women over age 35. Rule out a dominant breast mass.
• Patients should keep a diary of their breast pain superimposed on a record of their menstrual cycles, to help the clinician determine whether the pain is cyclic or non-cyclic.10
• Treatment for mastalgia in patients without a breast mass:
  —reassurance, support bra, low fat diet11
  —NSAIDs12
  —decrease or discontinue hormone replacement therapy in the postmenopausal woman
  —evening primrose oil: two capsules PO tid. Questionable efficacy but no severe side effects
  —tamoxifen, danazol, and bromocriptine may be helpful, but can have severe side effects13–16
  —patients with resistant or severe pain should be referred to a breast specialist.

Nipple discharge17,18

Introduction
• Most nipple discharge is benign. About 5% of women with nipple discharge have breast cancer. Older women with nipple discharge are more likely to have breast cancer than younger women.
• Nipple discharge can be physiologic or it can be caused by systemic hormonal disease or by intrinsic breast disease.
• Physiologic discharge is not spontaneous and comes from both breasts. It is not bloody. It is usually yellow to green in color.
• Nipple discharge which is spontaneous, not bloody, and from multiple ducts in both breasts in a non-pregnant, non-lactating woman is consistent with a systemic cause (hyperprolactinemia or hypothyroidism).
• Nipple discharge which is bloody, serosanguinous, or serous or discharge which comes from a single duct in one breast is consistent with intrinsic breast disease. In these cases, breast cancer must be ruled out.

Diagnosis

History
• Age; whether the discharge is spontaneous or contains blood; the presence or absence of menses in a premenopausal woman; pregnant or recently pregnant, breastfeeding, or ever pregnant; medication use such as dopamine blocking drugs; past breast disease; and cancer risk factors.

Physical examination
• Assess whether or not there is a breast mass. Note whether the discharge is spontaneous or must be expressed. Note whether the discharge comes from a specific duct or from multiple ducts. Note the color of the discharge and test for blood. Occult blood can be identified with a guaiac card.

10 Tavaf-Motamen H. Clinical evaluation of mastalgia. Arch Surg 1998;133:211–13. The author compared the accuracy of a pain diary using a visual analogue scale with a questionnaire based on patient recall. They found the diary to be more accurate.
15 O’Brien S, Abukhalil I. Randomized controlled trial of the management of premenstrual syndrome and premenstrual mastalgia using luteal phase-only danazol. Am J Obstet Gynecol 1999;180:218–23. This recent study showed that luteal phase-only danazol was effective for relief of premenstrual mastalgia.
16 Gately CA, Mansel RE. Management of the painful and nodular breast. Br Med Bull 1991;47:284–94. Danazol, bromocriptine or evening primrose oil can result in improvement in mastalgia in 77% of patients with cyclic mastalgia and 44% of patients with non-cyclic mastalgia.

About 70–85% of nipple discharges caused by cancer contain blood. Nipple discharges that are green, gray, black, or milky are not generally characteristic of breast cancer.
  • 37.9% papilloma; 28.9% cystic disease;
  • 16.2% mammary duct ectasia;
  • 13.8% breast cancer; 0.03% acute suppurative mastitis.
Assess for signs of infection. A complete neurological exam, including visual fields, should be done.

**Laboratory tests**
- Consider mammogram, prolactin, TSH, and other tests depending on the results of the history and physical examination.

**Galactorrhea**

**Definition**
- Milky, non-bloody discharge which comes from multiple ducts, usually bilateral and spontaneous, in a woman who is not breastfeeding. The presence of fat globules in the discharge distinguishes it from physiologic discharge.

**Etiology**
- Pituitary tumors; hypothalamic and other CNS disease; medications; hypothyroidism; chest wall lesions; breast stimulation; and idiopathic.

**Diagnosis**
- History, physical examination, prolactin level, TSH. If the prolactin is elevated, a MRI should be ordered to look for a pituitary tumor or other CNS lesion. A diagnostic workup for acromegaly and hypopituitarism is also indicated.
- Management of galactorrhea when the TSH, prolactin level, menses, and physical examination are normal except for galactorrhea: close follow up.

**Treatment of hyperprolactinemia**
- If possible, discontinue medications which can cause increased prolactin. (Many are psychotropic medications.)
- Isolated elevated prolactin levels and most pituitary adenomas can be treated with the dopamine agonists bromocriptine or cabergoline.
- Surgical treatment may be necessary for some macroadenomas.
- Hypothyroidism should be treated with thyroxine.

**Referral**
- If there is evidence of pituitary adenoma or other CNS pathology or the prolactin is severely elevated, refer to a specialist. Evidence of visual field defect or mass effect is an indication for urgent neurosurgical consultation.

**Serous or bloody or watery discharge**

**Etiology**
- Generally caused by intrinsic breast disease.
- Serous or bloody discharge is generally caused by intraductal papilloma/papillomatosis, duct ectasia, or intraductal cancer.
- Watery nipple discharge is generally caused by papilloma or cancer.

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Patients with galactorrhea and normal prolactin levels usually have normal menses and are fertile.

Patients with galactorrhea and elevated prolactin may have abnormal or absent menses and may be infertile.

**Etiology:** Pituitary tumors can secrete prolactin or growth hormone. Hypothalamic and other CNS disease can include CNS sarcoidosis and craniopharyngioma.

Drugs which can cause galactorrhea: phenothiazines, haloperidol, tricyclic antidepressants, oral contraceptives especially those with higher estrogen content, cimetidine, aldomet.

In hypothyroidism, elevated levels of thyrotropin releasing hormone (TRH) stimulate the anterior pituitary to produce excess prolactin.

Chest wall lesions can include surgery (post thoracotomy) and herpes zoster.

Other causes of hyperprolactinemia: chronic renal failure, cirrhosis.
Initial evaluation
- History, physical, mammogram.

Management
- Referral to a breast surgeon for further evaluation and possible duct excision.

Fibrocystic change
- “Change” rather than “disease,” since it is thought to result from an exaggeration of normal processes.
- Histologically present in about 90% of women and judged to be clinically present in about 50% of premenopausal women.
- Consists of epithelial proliferation, cysts, and fibrous tissue.

Presentation
- Painful, tender breasts with areas of thickening in premenopausal women. May be related to estrogen; areas of thickening and tenderness are greatest before and during the menses.

Evaluation if there is a dominant breast mass
- FNA; mammogram in women more than 35 years of age unless there is a cyst with non-bloody fluid which resolves completely after aspiration; core needle or excisional biopsy if there is still a possibility of breast cancer after FNA.

Management of fibrocystic change
- Reassurance and close follow up.
- When breast pain is the predominant symptom, treatment of mastalgia as discussed previously.
- Proliferative hyperplasia is associated with an increased risk for development of breast cancer; non-proliferative histology is not.\(^\text{21}\)

Management of cysts: FNA with or without a biopsy
- If the fluid is not bloody and the cyst completely resolves after aspiration, the patient should be re-examined in 4–8 weeks.
- If fluid has not reaccumulated and the physical examination is normal, the patient can be followed.
- If fluid has reaccumulated, the mass can be aspirated again. If fluid reaccumulates again or if the cyst does not completely resolve after initial aspiration, a biopsy is necessary.
- If the fluid is bloody, it should be sent for cytology and a biopsy should be done.

Fibroadenoma
- Is the most common benign solid tumor. It consists of fibrous tissue and epithelial components.
- Occurs mostly in premenopausal women, with a peak incidence in 20–25 year olds.

- Atypical hyperplasia on biopsy (4% of biopsies): 4–5 times increased risk for subsequent development of breast cancer.
- Hyperplasia without atypia (25%): 1.5–2 times increased risk.
- Non-proliferative or minimally proliferative fibrocystic change (68%): no increase.

Types of fibroadenoma include the common fibroadenoma, described as “fibroadenoma” in the text; the giant fibroadenoma which is more than 5 cm; the juvenile fibroadenoma; and phyllodes tumor. A cystosarcoma phyllodes tumor can occasionally be malignant, and, even if not malignant, can grow rapidly. All phyllodes tumors must be excised completely with histologically clear margins.
Typical presentation
- A single 1–4 cm non-tender mass which is firm, movable, and has a clear border. Hormonally sensitive. Often increases in size towards the end of the menstrual cycle or during pregnancy. Tends to regress in menopause but may increase in size in postmenopausal women on hormone replacement therapy.

Diagnosis
- FNA and/or biopsy, mammography in appropriate age range.

Treatment
- Excision or close clinical follow up.
- Complex fibroadenoma or fibroadenoma with proliferative change in the adjacent tissue can be associated with an increased risk of breast cancer. A simple fibroadenoma has no increased risk.22

Breast cancer
Epidemiology
Incidence and cumulative risk
- According to American Cancer Society estimates, there were 175,000 new cases of invasive breast cancer and 43,000 deaths from female breast cancer in 1999.23
- In women, breast cancer is the most common cancer diagnosis and the second most common cause of cancer death (after lung cancer).
- The cumulative risk of breast cancer in an average American woman over her lifetime, assuming that she lives to 85 years, is 12.5% or 1 in 8. This is the sum of the annual risks.

Risk factors
- Most women who develop breast cancer do not have risk factors other than being female.
- However, knowing whether a woman has risk factors can help direct screening and diagnostic efforts.
- Risk factors can be grouped according to the degree of risk. Some of the strongest risk factors are age, strong family history, atypical hyperplasia, lobular carcinoma in situ, and personal history of breast cancer. The following is adapted from Hulka.24

Strongest risk
- Age (old > young)27
- Country of birth (North America and Northern Europe > Asia and Africa)
- Atypical hyperplasia on biopsy21
- Two first degree relatives with breast cancer especially if bilateral or diagnosed before menopause


Definition of complex fibroadenoma: cysts are greater than 3 mm in diameter; or sclerosing adenosis; or epithelial calcification; or papillary apocrine changes.

Symptoms or concern about breast cancer are indications for excision of fibroadenoma. Some physicians follow patients with fibroadenoma, especially patients less than 25 years of age with small tumors that do not increase in size.


Most breast cancer (about 85%) occurs in women 50 and older. The relative risk of breast cancer in a 65–69 year old versus a 30–34 year old is about 17. At age 40, about 1 woman in 1000 is diagnosed with breast cancer each year. At age 60, about 1 woman in 400 is diagnosed with breast cancer per year.

24 Hulka BS, Stark AT. Breast cancer: cause and prevention. Lancet 1995; 346:883–7. These authors describe three groups of risk factors: the strongest have a relative risk greater than 4; moderate risk factors have a relative risk of 2.1–4; and the factors which increase risk somewhat have a relative risk of 1.1–2.
Moderate risk
- History of cancer in one breast
- Nodular densities covering more than 75% of the mammogram in a postmenopausal woman
- One first degree relative with breast cancer
- High dose radiation to the chest

Somewhat increased risk
- Hyperplasia on biopsy
- Age at first full term pregnancy 30 or greater
- Nulliparity
- Age at menarche less than 12 years
- Age at menopause 55 or older
- History of endometrial, ovarian, or colon cancer
- Alcohol consumption two or more drinks per day
- Postmenopausal obesity
- Hormone replacement therapy for more than five years

Genetics and breast cancer risk
- About 85% of breast cancer is sporadic.
- About 5–10% appears to be related to genetic mutations passed in a pattern of autosomal dominance, such as mutations of the BRCA1 and BRCA2 genes.
- About 5–10% of breast cancer may be hereditary but not related to specific inherited genetic mutations.
- BRCA1 on chromosome 17 and BRCA2 on chromosome 13 are both autosomal dominant genes that are thought to be tumor suppressor genes. Mutations in these two genes account for 80–90% of genetically transmitted breast cancer.
- The lifetime risk of breast cancer with a BRCA1 or BRCA2 mutation and a strong family history may be as high as 85%. In patients who are carriers of these genes without a strong family history, the risks are lower.
- Mutations of the BRCA1 gene also predispose women to ovarian cancer, with a lifetime risk as high as 65%, and predispose men to prostate and colon cancer. Mutations of the BRCA2 gene also predispose women to uterine cancer and predispose men to breast cancer, with a lifetime risk up to 6%, as well as prostate cancer.
- Genetic counseling with the option of a blood test for these genes can be suggested for women with personal or family histories of breast and/or ovarian cancer at a young age.

Risk modeling
- Several models have been developed for predicting risk. The Gail model is useful for calculating the risk of breast cancer in women who do not have strong family histories and who undergo regular mammographic screening. It calculates the risk for the next five years and until age 90 based on assessment of five risk factors.

31 Struewing JP, Hartge P, Wacholder S et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Engl J Med 1997;336:1401–8. Over 2 percent of Ashkenazi Jews carry either the 185delAG or the 5382insC mutation in BRCA1 or the 6174delT mutation in the BRCA2 gene. By the age of 70, the estimated risk of breast cancer was 56%.
The tamoxifen breast cancer primary prevention trial (BCPT P-1) used a version of the Gail model to determine eligibility for the trial. The ongoing Study of Tamoxifen and Raloxifene (STAR) primary prevention trial (BCPT P-2) uses the same version of the Gail model to determine eligibility.

Models are now being developed to assess risk in patients with the BRCA1 or BRCA2 genes.

### Incidence by pathology
Most breast cancer develops from proliferation of the epithelium lining the ducts or lobules, resulting in ductal or lobular breast cancer. The following percentages are approximate since the incidence of in situ carcinoma is increasing dramatically as a result of increased screening and detection.

- **Ductal** (85%)
  - Infiltrating ductal: 70%
  - Ductal carcinoma in situ (DCIS): 15%
- **Lobular** (14%)
  - Infiltrating lobular: 10%
  - Lobular carcinoma in situ (LCIS): 4%
- **Others**, including medullary, mucinous, papillary, and tubular (1%)

### Presentation
- About 40% of breast cancers present as a mass.
- Increasingly, breast cancer is being detected as an abnormality on mammogram without physical findings.
- Rarely, breast cancer presents as breast pain, nipple discharge, skin changes, or axillary adenopathy without a palpable mass.
- Invasive lobular carcinoma is more difficult to diagnose than invasive ductal carcinoma. It may present as a thickening or it may not be palpable. It may not be apparent on mammogram.
- Most DCIS presents as microcalcifications on mammogram without a palpable mass.
- The diagnosis of LCIS is made on biopsy which is done for other reasons. It is not palpable and cannot be seen on mammogram.

### Diagnosis
See prior discussion of evaluation of breast mass, breast pain, nipple discharge, and mammographic abnormality without an abnormal breast exam.

### Evaluation after tissue diagnosis
- Determine extent of disease with blood tests (CBC, LFTs, electrolytes) and chest radiograph.
- Bone scans and CT of chest and abdomen in clinically node negative patients only if the patient has relevant symptoms/signs or abnormal blood test results.
- Head CT only if the patient has neurologic findings.

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A copy of the Gail model may be obtained on disk from the National Cancer Institute.

The currently used staging system was described in the AJCC (American Joint Commission on Cancer) Staging Manual. Tumor size, nodal involvement, and metastasis determine the stage (0–IV).

- **T0**: No evidence of primary tumor
- **Tis**: tumor in situ
- **T1**: 2 cm or less
- **T2**: More than 2 and less than 5 cm
- **T3**: More than 5 cm
- **N0**: no nodes
- **N1**: presence of movable ipsilateral axillary lymph node
- **N2**: presence of ipsilateral axillary lymph node fixed to another lymph node or structure
- **N3**: presence of ipsilateral internal mammary lymph node
- **M0**: No distant metastasis
- **M1**: Distant metastasis (includes metastasis to ipsilateral suprACLavicular lymph node or internal mammary lymph node)
- **Stage 0**: Tis, N0, M0 (ductal carcinoma in situ)
- **Stage I**: T1, N0, M0
- **Stage IIA**: T0, N1, M0 or T1, N0, M0 or T2, N0, M0
- **Stage IIB**: T2, N1, M0 or T3, N0, M0
- **Stage III**: locally advanced
- **Stage IV**: metastatic

**Prognostic factors**: include lymph node status, tumor size, the presence or absence of estrogen and progesterone receptors, and tumor grade. Other factors are being studied, including HER-2/neu, epidermal growth factor receptor family, S-phase, DNA ploidy, angiogenesis, bone marrow micrometastases, and others.
Staging is based on tumor size, node involvement, and metastasis and is described as stages 0–IV.

**Stage I and II invasive breast cancer: treatment**

*Mastectomy or lumpectomy and radiation therapy*

- Patients treated with lumpectomy require postoperative radiation therapy to the breast. The combination of lumpectomy and radiation therapy is referred to as breast conservation therapy.
- Both breast conservation therapy and mastectomy have the same overall survival rates if the cancer is unifocal, can be excised with clear margins, and does not have an extensive intraductal component. The local recurrence rate with breast conservation therapy is usually 5–10%.
- Mastectomy is preferable when the tumor is multifocal, unable to be excised with clear margins, or when there is an extensive intraductal component.

**Axillary node dissection**

- Is done to determine involvement of lymph nodes, which in turn determines prognosis and treatment.
- Some surgeons perform sentinel lymph node mapping (SLN) for patients who have extensive or high grade DCIS, or a T1 or small T2 tumor, and a clinically negative axillary exam. If the sentinel node is negative for metastasis, further axillary dissection is not necessary. If the sentinel node is positive for metastasis, axillary node dissection is necessary.

**Adjuvant radiation to the chest wall after mastectomy**

- Decreased local recurrence and improved survival in patients at high risk for local or regional recurrence in several trials.
- Recommended for patients with a locally advanced primary tumor (large or involving skin or muscle) or with four or more positive lymph nodes.

**Adjuvant chemotherapy**

- Recommended for women with breast cancer greater than 1 cm, up to age 70, regardless of nodal status or menopausal status.
- Four to six months of chemotherapy are as effective as longer courses.
- May be combined with adjuvant hormonal therapy.

**Adjuvant hormonal therapy – tamoxifen**

- Acts as an estrogen antagonist on the breast and as an estrogen agonist on the heart, bones, and uterus.
- Recommended for five years for women who have breast cancer receptors positive for estrogen, regardless of nodal or menopausal status.
- Risks include increased risk of endometrial cancer, rare thromboembolic disease, and rare retinopathy. Side effects

**References**


Two or more agents are given. Regimens including an anthracycline (doxorubicin) are more effective than those without. Currently accepted regimens include AC, CAF, CMF: C = cyclophosphamide (Cytoxan) M = methotrexate F = 5-fluorouracil A = doxorubicin (Adriamycin)

Studies are ongoing to study the addition of taxanes in node positive breast cancer.
of tamoxifen include hot flashes, vaginal discharge, and depressed mood.
- May be combined with adjuvant chemotherapy.

**Ductal carcinoma in situ (DCIS)**\(^{44,45}\)

**Definition and characteristics**
- Ductal carcinoma confined to the ducts.
- More common than LCIS.
- Most DCIS presents as microcalcifications on mammogram without a palpable mass. It occasionally presents as a palpable breast mass.
- Can have associated microinvasion.

**Treatment**
- Mastectomy is the preferred surgical option for lesions larger than 5 cm and in patients with DCIS in more than one area of the breast.
- Wide excision followed by radiation therapy is an alternative to mastectomy for smaller lesions.\(^{46,47}\)
- Axillary node dissection is not usually done after lumpectomy for small DCIS lesions without invasion. Superficial axillary dissection is added to mastectomy for large DCIS lesions if an invasive component is found.
- One trial showed that tamoxifen after lumpectomy and radiation decreased the rate of subsequent breast cancer. There was no effect on survival.\(^{48}\)

**Lobular carcinoma in situ (LCIS)**

**Definition and characteristics**
- Tends to be multicentric, multifocal, and bilateral.
- Most often found in premenopausal women.
- Often not palpable on physical examination and not detectable on mammogram.
- Diagnosed on breast biopsy done for other reasons.
- Is a risk factor (marker) for the future development of invasive breast cancer, either ductal or lobular, in either breast. The relative risk is 7–12 times that of the general population.

**Management options for LCIS and other high risk patients**
- Close surveillance, with physical examination two to three times a year and annual mammograms starting at an early age.
- Chemoprevention. Tamoxifen has been approved by the FDA for prevention of breast cancer in high risk patients on the basis of the BCPT P-1 trial mentioned earlier.\(^{34}\) High risk patients can also enroll in clinical trials, such as the ongoing STAR trial.
- Prophylactic bilateral total mastectomy may reduce the risk of breast cancer by 85–90% in high risk patients.\(^{49-51}\) It is important to note that it does not reduce the risk by 100%, since not all breast tissue can be removed by surgery.
Follow up of the breast cancer patient

*Evaluation and surveillance*  
- The suggested regimen is history and physical exam every 3–6 months for the first three years, then every 6–12 months for the next two years, and then annually, plus...
- Annual mammogram.
- Evaluation for symptoms of depression and anxiety and referral for psychotherapy and/or cognitive behavioral therapy as indicated. Many patients find breast cancer support groups helpful as well.
- Evaluation of menopausal symptoms as indicated (see below).
- For postaxillary node dissection patients, evaluation for lymphedema (see below).
- For postsurgical patients: assessment of range of motion of the ipsilateral shoulder and referral for physical therapy as needed.
- Regular gynecologic evaluation, especially in patients on tamoxifen. Although tamoxifen is a risk factor for endometrial cancer, it is not currently recommended that patients on tamoxifen have periodic transvaginal ultrasounds or endometrial biopsies, unless they have vaginal bleeding.
- **Not recommended** unless patients have symptoms or signs: blood tests (including tumor markers), chest radiograph, bone scan, liver ultrasound, or CT scans.

**Lymphedema**  
- Postaxillary node dissection patients should be assessed for swelling of the ipsilateral arm (lymphedema). Both preoperative and postoperative measurements of the arms should be done.
- Lymphedema occurs in 6–30% of breast cancer survivors. It is related to the extent of axillary node dissection and is worsened by heavy lifting and by trauma to the upper extremity.
- Patients need to be educated about preventive measures: no heavy lifting; no blood pressures, injections, or intravenous lines in the upper extremity; immediate use of a topical antiseptic and/or antibiotic if there is even a minor injury to the upper extremity; and immediate medical attention if swelling develops. Weight control is also important. Lymphedema tends to be worse in the obese patient.
- Consider treatment when measurements of the two arms differ by more than 2.0 cm. Once lymphedema has developed, the patient can be fitted for a compression sleeve, which should be worn regularly. The patient can also be referred to a center specializing in lymphedema for physiotherapy.

**Menopause**  
- Postmenopausal patients should undergo evaluation of menopausal symptoms, including hot flashes, insomnia, vaginal dryness, dyspareunia, urinary urgency, and frequency.
These symptoms may be more severe in patients who are newly menopausal secondary to chemotherapy and patients who are taking tamoxifen.

Estrogen replacement therapy traditionally has not been used in breast cancer survivors. Now, however, more trials are being conducted on the use of HRT in these patients\textsuperscript{56,57} and some specialists are using HRT in selected breast cancer survivors.

Clonidine tablets 0.1 mg PO qd and clonidine patch 100 mg q week have also been shown to be useful in patients with hot flashes, including those patients taking tamoxifen.\textsuperscript{58} Venlafaxine and paroxetine have also been shown in pilot studies to be useful for hot flashes in breast cancer survivors.\textsuperscript{59,60}

Postmenopausal patients should undergo evaluation for osteoporosis and coronary heart disease. These patients should also be counseled about preventive measures, including calcium, diet, and exercise.


8 Cancer screening

Nate Link

Introduction

Characteristics of “screenable” cancers
- Are relatively common (lung)
- Cause significant morbidity and mortality (breast)
- Are treatable if detected early (prostate)
- Are incurable if detected late (colon)
- Have relatively long latent periods (cervical)
- Have acceptable screening tests (all of the above)

Characteristics of acceptable screening tests
- Are relatively inexpensive (PSA)
- Are adequately sensitive (stool guaiac at 70–80%)
- Are highly specific (mammography at 95–98%)
- Are acceptable to patients (Pap test)
- Are widely available (all of the above)

Definitions
- Interval cancers are those that become clinically evident between screening. They are defined as false negative results (cancers that were missed on the previous screen) and represent failures of a screening program. They are used to calculate sensitivity.
- Sensitivity of a screening test is defined as the number of cancers detected through screening divided by the total number of cancers that are diagnosed (screen detected plus interval cancers) over a given period. A screening test that is 80% sensitive would be expected to generate an interval cancer rate of 20%.
- Specificity of a screening test is the probability that a healthy (non-cancerous) subject will have a negative test result. Specificity is extremely important in a screening test. Even highly specific screening tests such as mammography lead to many unnecessary biopsies because the prevalence of disease is so low.

General principles of screening
- The prevalence screen is a patient’s first encounter with a screening test. It provides the highest yield because it captures cancers that have been latent for years. It also generates the highest number of false positives.
- Incidence screens provide lower yields because they only capture cancers that have become newly detectable since the previous screen. They also produce fewer false positives because abnormalities picked up on the prevalence screen (such as a benign breast lesion) have already been identified.

Glossary
PSA = prostate specific antigen
Pap test = Papanicolaou (cervical) smear
FOBT = fecal occult blood (guaiac) test

Ten Leading Causes of Cancer Death in Men and Women in US, 1999:

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Lung</td>
<td>31%</td>
<td>1. Lung 25%</td>
</tr>
<tr>
<td>2. Prostate</td>
<td>13%</td>
<td>2. Breast 16%</td>
</tr>
<tr>
<td>3. Colon</td>
<td>10%</td>
<td>3. Colon 11%</td>
</tr>
<tr>
<td>4. Pancreas</td>
<td>5%</td>
<td>4. Pancreas 5%</td>
</tr>
<tr>
<td>5. NHL</td>
<td>5%</td>
<td>5. Ovary 5%</td>
</tr>
<tr>
<td>6. Leukemia</td>
<td>4%</td>
<td>6. NHL 5%</td>
</tr>
<tr>
<td>7. Esophagus</td>
<td>3%</td>
<td>7. Leukemia 4%</td>
</tr>
<tr>
<td>8. Liver/Bile</td>
<td>3%</td>
<td>8. Uterus 2%</td>
</tr>
<tr>
<td>10. Stomach</td>
<td>3%</td>
<td>10. MM 2%</td>
</tr>
<tr>
<td>All Other</td>
<td>25%</td>
<td>All Other 21%</td>
</tr>
</tbody>
</table>

(NHL = Non-Hodgkin’s lymphoma, MM = multiple myeloma)
In 1995, cancer accounted for 23.3% of all deaths in the US, second only to heart disease (31.9%).

Definition of screening sensitivity
Strictly speaking, a false negative screening result would be one that misses any cancer, regardless of how small (even at the four cell stage). This would produce low sensitivities for many tests. For practical purposes, however, a cancer is not considered to have been missed by screening unless it becomes clinically evident before the next screen (i.e., an interval cancer). This gives an annual screening program several opportunities to detect a given cancer before it becomes symptomatic.

In general, prevalence screens for breast cancer tend to identify three times as many cancers as subsequent annual (incidence) screens. This suggests that the average sojourn time (from the point of detectability to clinical symptoms) is about three years.

Continued
CANCER SCREENING

Costs of screening programs tend to be high. Although some programs (for example, breast and colon cancer) have been shown to save lives, they do not save money. The net economic costs must be weighed against net clinical benefits.

Breast cancer

Epidemiology and overview

- In 1999, the estimated number of newly diagnosed breast cancer cases in the US was 176,000 and the estimated number of breast cancer deaths was 43,700.¹
- For a woman, the most important risk factor for breast cancer is age. The cumulative risk of developing breast cancer in the first four decades of life is 0.43%. The risk during the two decades from age 60–79 is 6.9%. The lifetime risk is 12.5% or 1 in 8.¹
- The three leading options for breast cancer screening are mammography, clinical breast exam by the physician, and self-breast exam by the patient.
- Mammography is by far the most extensively studied of the three options. Clinical breast exam and breast self exam have never been compared to usual care in a randomized trial.
- The medical community has achieved consensus on the efficacy of mammography screening for women aged 50–74.
- For women under 50 or over 74, the debate continues (see below).

Accuracy of mammography screening

- The sensitivity and specificity of mammography screening are approximately 75–80% and 95% respectively.²
- In a mobile mammography screening program in San Francisco, the experiences of about 32,000 women were reviewed. The results of the first screen were as follows.

Yield of the First (Prevalence) Screen³

<table>
<thead>
<tr>
<th>Yield</th>
<th>Age group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal mammograms per 1000</td>
<td>30–39</td>
</tr>
<tr>
<td></td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>40–49</td>
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<td></td>
<td>63</td>
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<td></td>
<td>50–59</td>
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<td></td>
<td>66</td>
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<tr>
<td></td>
<td>60–69</td>
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<tr>
<td></td>
<td>78</td>
</tr>
<tr>
<td>Biopsies per 1000 mammograms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>16</td>
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<tr>
<td></td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>26</td>
</tr>
<tr>
<td>Cancers per 1000 mammograms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>3</td>
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<tr>
<td></td>
<td>6</td>
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<tr>
<td></td>
<td>13</td>
</tr>
<tr>
<td>PPV of abnormal mammogram</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>17%</td>
</tr>
<tr>
<td>Cancers per 100 biopsies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>17</td>
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<tr>
<td></td>
<td>30</td>
</tr>
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<td></td>
<td>46</td>
</tr>
</tbody>
</table>

Note the increasing positive predictive value of an abnormal mammogram with increasing age. Note also the increasing yield of biopsy with increasing age.

-one of the most useful outcome measures is number of screenings per life saved, but this is often not explicitly provided in reports of randomized trials.

Observational studies are generally insufficient to evaluate screening programs. Assessment of benefits requires large randomized trials comparing outcomes.

The cumulative risk for breast cancer in a woman during her 40s is 16 per 1000 over 10 years.

Mammography benefit simplified

In an average cohort of 2000 women aged 60, approximately six new cancers will occur annually. Of these, three would be expected to be cured whether the women were screened or not. Another two would be expected to be ultimately fatal regardless of screening. The final one case can be converted from a death to a survival through the benefit of screening. Thus screening may produce a relative reduction in mortality of 33% (from three to two deaths), and an absolute risk reduction of one life saved per 2000 screenings.

² Kavanagh AM, Mitchell H, Giles GG. Hormone replacement therapy and accuracy of mammographic screening. Lancet 2000;355:270–4. A study of mammography results in about 103,000 women. Sensitivity of mammography when performed at two year intervals was 77% in HRT non-users and 65% in HRT users. Specificity was 95% and 94% respectively.

³ Kerlikowske K, Grady D, Barclay J et al. Positive predictive value of screening mammography by age and family history of breast cancer. JAMA 1993;270:2444–50. A review of outcomes from a true life screening program. In this study, annual follow up (incidence) screens yielded about a third as many cancers each as the prevalence screens.
• In the same study, the yield of mammography was compared in women with and without positive family histories.

Positive Predictive Value of Mammography by Family History³

<table>
<thead>
<tr>
<th>Family history</th>
<th>30–39</th>
<th>40–49</th>
<th>50–59</th>
<th>&gt;59</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>2%</td>
<td>5%</td>
<td>9%</td>
<td>17%</td>
</tr>
<tr>
<td>Positive</td>
<td>4%</td>
<td>13%</td>
<td>22%</td>
<td>18%</td>
</tr>
</tbody>
</table>

• Note that a positive family history shifts the yield curve downward, suggesting the need to screen about one decade earlier in high risk women.

False positive rates
• In an HMO screening program of 2400 women aged 40–69 at entry, outcomes were observed over a 10 year period.⁴
• The estimated cumulative incidence of a false positive result was 49% after 10 mammograms and 22% after 10 physical exams.
• During 10 years of screening, a woman had a 19% cumulative probability of undergoing a breast biopsy.

Effectiveness of mammography screening
• Mammography is the best studied of all screening tests. At least eight large randomized trials have been conducted. Nearly all of them show a reduction in breast cancer mortality in certain age groups.
• The conclusions of these studies have been hotly debated, especially those of women under 50. One recent article identified randomization irregularities in almost all the trials.⁵

Health Insurance Plan of New York trial⁶
• Conducted in the 1960s, the first major trial of cancer screening.
• About 60000 women aged 40–74 were randomized to screening with mammography plus clinical exam versus usual care.
• Treatment patients received about four screenings on average over a five year period.
• Over 18 years, breast cancer mortality decreased by 24% in the screened group.
• About 2000 screenings were required for each life saved.

Swedish trials⁷
• Five randomized trials conducted in the 1970s.
• Women aged 40–74 were randomized to single view or two view mammography screening every 18–33 months versus usual care. On average, women underwent 2–5 rounds of screening.
• Between the five studies, more than 280,000 women were enrolled and followed for 9–11 years.
• Screened women aged 50–69 experienced a 29% reduction in mortality. Screened women aged 40–49 experienced a 13% reduction in mortality.

**Canadian National Breast Screening Study: women 50–59 years**
• About 40,000 women were randomized to annual mammography versus no mammography. Women in both arms received annual clinical breast exams.
• Women in the screening group underwent an average of 4–5 screenings apiece.
• Over seven years of follow up, there was no advantage noted in the mammography group (RR for breast cancer mortality = 0.97).
• This is the only study that directly assessed mammography as an adjunct to clinical breast exam.

**Canadian National Breast Screening Study: women 40–49 years**
• About 50,000 women were randomized to annual mammography plus clinical breast exam versus usual care.
• After 10.5 years of follow up, women in the screening group experienced a non-significant increase in breast cancer mortality after 10.5 years of follow up (RR = 1.14, P = NS).
• This was the only trial specifically designed to assess the benefit of screening women in this age group.

**Summary and conclusions**
• Multiple trials demonstrated a benefit of screening versus no screening especially in women aged 50–74. In this age group the expected benefit is approximately a 25–30% RRR in breast cancer mortality or one life saved per 2000 mammograms.
• For women aged 40–49, the studies suggest a RRR of 18% or about one life saved per 5000 to 10,000 mammograms. There is no consensus on the value of screening in this age group.
• For women 75 and over there are no reliable data.
• Most of the major trials which demonstrated a mammography benefit performed screenings at intervals ranging from 18 to 33 months. There is no direct evidence to support an interval of 12 months.
• Although clinical breast exams have received less emphasis, combining mammography with clinical breast examination improves the sensitivity of screening, especially in women under 50. Some investigators have suggested the need for annual clinical exams in this age group.

**Cervical cancer**

**Epidemiology**
• Cervical cancer is essentially an infectious disease. About 90% of cases of cervical neoplasia are associated with human papilloma virus (HPV)."}

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8 Miller AB, Baines CJ, To T, Wall C. Canadian National Breast Screening Study: 2. Breast cancer detection and death rates among women aged 50–59 years. Can Med Assoc J 1992;147:1477–88. Of 135 cancers detected at the baseline screen, 46% were detected by mammography alone, 30% by both mammography and clinical exam, and 24% by clinical exam alone.


13 Baines CJ, Miller AB. Mammography versus clinical examination of the breasts. J Natl Cancer Inst 1997;22:125–9. Interestingly, mammography has never been compared head to head with clinical breast exams, and clinical breast exams have never been compared to usual care.

In 1999, the estimated number of newly diagnosed cervical cancer cases in the US was 12,800 and the estimated number of cervical cancer deaths was 4,800.\cite{Eddy}

Without screening, an average 20 year old woman has a 2.5% lifetime risk of developing invasive cervical cancer and a 1.2% lifetime risk of dying from cervical cancer.\cite{Nanda}

In conjunction with implementation of the Papanicolaou (Pap) test as a standard screening modality, cervical cancer mortality declined from a rate of 14.2 per 100,000 women per year in 1973 to 7.8 per 100,000 women per year in 1994.\cite{LaVecchia} Most women who died of cervical cancer had never had a Pap test.

Overview
- Cervical cancer is the classic screenable disease.
- Its accessibility to detection in the precancerous stage has fostered widespread use of the relatively simple and inexpensive Pap test.
- Its naturally slow progression has permitted multiple opportunities for identification of lesions in their early stages.
- The development of acceptable techniques for follow up and treatment (colposcopy and conization) has permitted adequate control of the disease in its premorbid state. In this manner, Pap testing is actually an exercise in the prevention of cervical cancer.

Accuracy and effectiveness of Pap testing
- The accuracy of the Pap test has been assessed in many studies of varying quality. A recent meta-analysis estimated the overall sensitivity for cervical intraepithelial neoplasia, grade II–III lesions to be 58%. Specificity was 92%.\cite{Nanda}
- Because the Pap test has become so widely accepted as a standard of care, there has never been, and never will be, a randomized trial comparing Pap tests to usual care. The main point of contention is the frequency of screening (see below).

Frequency of Pap testing
- Multiple case control studies have demonstrated a protective effect that varies with the frequency and timing of the test.
- For example, in one study, investigators estimated that the incidence of invasive cancer could be reduced 64% by screening every five years, 82% by screening every three years, and 90% by screening even more often than every three years.\cite{LaVecchia}
- In a classic review of this subject, the reduction in the lifetime cumulative incidence of cervical cancer was estimated:\cite{Eddy}

<table>
<thead>
<tr>
<th>Screening schedule</th>
<th>Reduction in rate</th>
<th># of Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 35–64, q 5 years</td>
<td>69.6%</td>
<td>6</td>
</tr>
<tr>
<td>Age 20–64, q 5 years</td>
<td>83.6%</td>
<td>9</td>
</tr>
<tr>
<td>Age 20–64, q 3 years</td>
<td>91.2%</td>
<td>15</td>
</tr>
<tr>
<td>Age 20–64, q 1 year</td>
<td>93.3%</td>
<td>45</td>
</tr>
</tbody>
</table>

The lower than expected sensitivity is balanced by the opportunity for multiple evaluations over many years of typically slow cervical cancer progression.

By the same reasoning, screening 10,000 women every two years instead of every three years over a 55 year period would prevent one additional cervical cancer death at a cost of 180,000 extra Pap tests.
Note that the extra 30 tests performed by screening annually as opposed to every three years only added 2% in efficacy.

Continuing screening every three years at age 65 was estimated to save 18 additional lives for every 10,000 women participating. The extension of screening beyond age 65 was much more efficacious than decreasing the screening interval.

The cost of each year of life added by cervical cancer screening in women over 65 was estimated to be less than that for pneumococcal vaccine, mammography, and hypertension monotherapy.18

Summary and conclusions

Observational studies have consistently supported the effectiveness of Pap tests for all women over 20 years of age.

Because of the slow progression of cervical neoplasia, nearly all the potential benefit is achieved by screening every three years.

Extending testing to women over the age of 65 is believed to be more cost effective than increasing the frequency of screening in women under 65.

Colorectal cancer

Epidemiology and overview

In 1999, the estimated number of newly diagnosed colorectal cancer cases in the US was 133,000 and the estimated number of colorectal cancer deaths was 57,000.1

The most important risk factor for colorectal cancer is age. The cumulative risk of developing colorectal cancer in the first four decades of life is 0.06%. The risk during the two decades from age 60–79 is 3.1% for women and 4.1% for men. The lifetime risk is 5.7% or 1 in 18.1

There is a growing consensus that men and women over 50 should undergo colorectal cancer screening with either fecal occult blood testing (FOBT), sigmoidoscopy, colonoscopy or a combination thereof.

The exact type of screening is open to debate (see below).

Minnesota Colon Cancer Control Study

Patients aged 50–80 who were offered annual FOBT screening using Hemoccult II slides (mostly rehydrated) experienced 33% fewer deaths from colorectal cancer than control patients.

About three lives were saved for every 1000 patients over 15 years.

About 2800 screenings and 130 colonoscopies were required for each life saved; 38% of all subjects underwent colonoscopy at some point during the study.

A second treatment group receiving biennial screening showed no benefit of screening.

Overall mortality was unaffected.


Some experts recommend annual screening for women at higher risk (for example, multiple sexual partners).

19 Mandel JS, Bond JH, Church TR et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. N Engl J Med 1993;328:1365–71. For colorectal cancer, the positive predictive value for rehydrated slides was 2.2% meaning that 98% of positive screens were false positives. The positive predictive value for polyps was 27.5%.

A follow up article from the Minnesota study reported the probability of finding either colorectal cancer or a large adenomatous polyp (>1 cm) in relation to the number of positive Hemoccult slides (out of 6):

<table>
<thead>
<tr>
<th>No. + slides</th>
<th>% CRC</th>
<th>% large polyp</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.87</td>
<td>5.99</td>
</tr>
<tr>
<td>2</td>
<td>1.55</td>
<td>6.08</td>
</tr>
<tr>
<td>3</td>
<td>1.16</td>
<td>7.03</td>
</tr>
<tr>
<td>4</td>
<td>1.93</td>
<td>7.49</td>
</tr>
<tr>
<td>5</td>
<td>2.72</td>
<td>8.25</td>
</tr>
<tr>
<td>6</td>
<td>4.53</td>
<td>7.87</td>
</tr>
</tbody>
</table>

Mandel JS, Church TR, Bond JH et al. The effect of fecal-occult blood screening on the incidence of colorectal cancer. N Engl J Med 2000;343:1603–7. This article also showed that colorectal cancer incidence declined by 20% in the screened group during 18 years of follow up, suggesting a “preventive effect” by identifying and removing adenomas.
Note that colorectal cancer accounted for about 3% of overall mortality.

When slides were hydrated, sensitivity increased from 81% to 92% but the marginal increase in detected cancers came at the unacceptable cost of quadrupling the positivity rate from 2.4% to 9.8% of all screenings.

**British trial of biennial screening**
- Patients aged 50–74 who were offered screening every other year by non-rehydrated Hemoccult testing experienced a 15% reduction in colorectal cancer deaths.
- Total mortality was unaffected.
- About one life was saved for every 10,000 patient years of follow up (about half the benefit of the Minnesota study).
- More than 40% of subjects offered screening did not accept.

**Numbers of Events per 10,000 Patient Years**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Annual</th>
<th>Biennial</th>
<th>No screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRC cases</td>
<td>23</td>
<td>23</td>
<td>26</td>
</tr>
<tr>
<td>CRC mortality</td>
<td>5.9</td>
<td>8.3</td>
<td>8.8</td>
</tr>
<tr>
<td>Total mortality</td>
<td>216</td>
<td>218</td>
<td>216</td>
</tr>
</tbody>
</table>

**Danish trial of biennial screening**
- Subjects aged 45–75 who were offered non-rehydrated Hemoccult II testing every other year experienced an 18% decrease in colorectal cancer mortality.
- About 2000 screenings and 20 colonoscopies were required for each colorectal cancer death prevented. This represented the highest efficiency of all three studies.
- Only about 1% of Hemoccult screenings were positive.
- On the first screening, 17% of positive results were confirmed as cancer and 32% were confirmed adenomas \( \geq 1 \) cm. This was a much higher yield than the Minnesota study (about 2% and 6% respectively).

**Screening sigmoidoscopy**
- Theoretically attractive as a **preventive** measure: adenomas may be identified and removed before they progress to cancer.
- Only about half of all colorectal cancers are within the reach of a 60 cm flexible sigmoidoscope.
- The benefits of sigmoidoscopy have not yet been assessed by a randomized trial, although at least one major trial is under way.

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20. Hardcastle JD, Chamberlain JO, Robinson MHE et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet 1996;348:1472–7. Subjects with less than 5/6 positive guaiac samples received a second screening before initiating colonoscopy. Only 4% of all subjects underwent a colonoscopy, compared to 38% in the Minnesota trial. The positive predictive value was 12% for colorectal cancer and 46% for all neoplasia.

• A well designed case control study suggested a 60% reduction in the incidence of death from colorectal cancer within reach of a sigmoidoscope. The protective effect appeared to hold for 10 years after the procedure. If true, this would save the same number of lives as the Minnesota trial of FOBT (3 per 1000 over 10 years).
• Colonoscopy could theoretically double the benefit to 60% reduction in mortality of all colorectal cancer, but would more than double the cost and risk of screening.

Summary and conclusions
• Fecal occult blood testing unequivocally decreases colorectal cancer mortality.
• Screening annually with rehydrated guaiac cards provides the greatest benefit (RRR = 30%) at a very high cost (2800 screenings and 130 colonoscopies for every life saved).
• Screening biennially with non-rehydrated cards is less beneficial (RR = 18%) but more cost effective (2000 screenings and 20 colonoscopies per life saved).
• Observational studies strongly support the effectiveness of sigmoidoscopy as a preventive modality, but this has not yet been confirmed by randomized trials.
• Many experts recommend annual FOBT and sigmoidoscopy screening every 5–10 years.

Lung cancer
Epidemiology and overview
• Lung cancer is by far the leading cause of cancer death in both men and women in the US.
• In 1999, there were an estimated 171,600 new cases of lung cancer and 158,900 deaths from lung cancer in the US.1
• Besides smoking, the most important risk factor for lung cancer is age. The cumulative risk of developing lung cancer in the first four decades of life is less than 0.05%. The risk during the two decades from age 60–79 is 6.6% for men and 4.0% for women. The lifetime risk is 8.3% for men, or 1 in 12, and 5.6% in women, or 1 in 18.1
• Current options in lung cancer screening include periodic chest films, sputum cytology, or low-dose helical CT scans.

The Mayo Lung Project23
• This, the largest trial ever conducted for lung cancer screening, randomized 9200 male smokers to receive chest radiographs and sputum cytology every four months for six years. The usual care arm was advised to obtain these tests annually.
• After 20 years of follow up, lung cancer mortality was 4.4 deaths per 1000 patient years in the intervention group and 3.9 deaths per 1000 patient years in the control group.
• The authors concluded that there was no benefit to the intervention.

22 Selby JV, Friedman GD, Quesenberry CP, Weiss NS. A case-control study of screening sigmoidoscopy and mortality from colorectal cancer. N Engl J Med 1992;326:653–7. The conclusions were strengthened by the observation that sigmoidoscopy was not associated with a reduction in mortality beyond the reach of a sigmoidoscope.

Early Lung Cancer Action Project (ELCAP)\textsuperscript{24}

- 1000 asymptomatic volunteer men and women smokers (on average, 67 years old and 45 pack years) underwent a single round of chest radiographs and a helical low-dose CT scan. The CT images were obtained of the entire lung area in a single breath hold.
- If between one and six non-calcified nodules were identified, the CT was classified as positive and the subject underwent high resolution CT scanning with serial follow up or biopsy as indicated.
- In 233 subjects, 363 non-calcified nodules were identified. (Only 33 of these subjects had nodules identified by plain films.)
- In 28 subjects, follow up evaluation led to a biopsy. In 27 of these, the nodule was malignant. In 26 of these, the tumor was resectable (23 were stage I).
- The authors concluded that low dose CT scanning is an effective method to detect early stage (resectable) lung cancer. Further follow up of the subjects is under way.

Summary and conclusions

- The only large trial of chest radiographs and sputum cytology failed to show any benefit in smokers.
- The use of low dose helical CT scanning is a promising technology that is effective in identifying early stage lung cancer in smokers.

Ovarian cancer

Epidemiology and overview

- In 1999, the estimated number of newly diagnosed ovarian cancer cases in the US was 25,200 and the estimated number of ovarian cancer deaths was 14,500.\textsuperscript{1}
- The main options for ovarian cancer screening include clinical examinations, transvaginal ultrasonography, and tumor markers.

Effectiveness of screening

- The pelvic examination is of limited value in ovarian cancer screening because lesions large enough to be detected have usually disseminated. It is estimated that 10,000 pelvic examinations are required to detect a single case of early stage ovarian cancer.\textsuperscript{25}
- In a recent study of transvaginal ultrasonography, 51,550 women received an initial screen, followed by further evaluation if abnormal.\textsuperscript{26} A total of 22 primary cancers were detected (77% in Stage I). For every cancer detected, there were 2500 initial screens, 260 secondary screens, and 15 laparotomies. The effect on outcome is unknown.
- CA-125 is a tumor marker for epithelial ovarian cancers. A level greater than 35 micrograms/ml is usually considered

\textsuperscript{24} Henschke CI, McCauley DI, Yankelevitz DI et al. Early Lung Cancer Action Project: overall design and findings from baseline screening. Lancet 1999;354:99–105. Suspicious lesions <6 mm were followed serially for evidence of growth. Lesions >10 mm were biopsied. Follow up of lesions 6–10 mm varied per clinical judgment. Of the 27 malignancies detected, 18 were adenocarcinomas and only one was a squamous cell carcinoma.

In 20/27 malignancies, the chest film failed to identify the lesion.

The study protocol led to the identification of 27 malignancies in only 28 biopsies, an unprecedented degree of efficiency for a screening test. The extremely high sensitivity of the screening modality permitted following lesions over time for evidence of growth. Non-growing lesions were not biopsied.

Unlike prostate cancer, lung cancer lesions are believed to lead to clinically evident disease nearly 100% of the time.


positive. However, the CA-125 level is relatively inaccurate for early stage tumors. Only about half of patients with Stage I ovarian cancers have elevated CA-125 and many benign conditions cause false positive results.

Summary and conclusions
- A suitable screening test for ovarian cancer has not yet been identified. The lower incidence of ovarian cancer mortality (a third of that for breast cancer) requires a greater investment in screening to prevent a cancer death.
- The use of transvaginal ultrasonography and CA-125, possibly in combination, is still under investigation.

Prostate cancer

Epidemiology and overview
- In 1999, the estimated number of newly diagnosed prostate cancer cases in the US was 179,300 and the estimated number of prostate cancer deaths was 37,000.1
- The most important risk factor for prostate cancer is age. The cumulative risk of developing prostate cancer in the first four decades of life is less than 0.01% (1 in 10,000). The risk during the two decades from age 60–79 is 14.8%. The lifetime risk is 17.0% or 1 in 6.
- The incidence in black men is about 60% higher than the risk in white men.28
- The age adjusted incidence of prostate cancer is 80-fold greater in the US than China.1 This is mostly due to differences in case finding.
- Based on autopsy studies, the prevalence of histologic prostate cancer is estimated to be about 30% in men over 50.28
- Before the advent of prostate specific antigen (PSA), the lifetime risk for prostate cancer was 10% and for prostate cancer death 3%.29 Before PSA about 2/3 of prostate cancers never came to light.

Age Specific Prevalence of Prostate Cancer: Autopsy Studies30

<table>
<thead>
<tr>
<th>Age</th>
<th>Tumor &lt; 0.5 ml</th>
<th>Tumor &gt; 0.5 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–49</td>
<td>7.2%</td>
<td>4.8%</td>
</tr>
<tr>
<td>50–59</td>
<td>9.0%</td>
<td>6.0%</td>
</tr>
<tr>
<td>60–69</td>
<td>13.2%</td>
<td>8.8%</td>
</tr>
<tr>
<td>70–79</td>
<td>23.4%</td>
<td>15.6%</td>
</tr>
<tr>
<td>&gt; 80</td>
<td>25.8%</td>
<td>17.2%</td>
</tr>
</tbody>
</table>

- Between 1984 and 1992, the incidence rate of prostate cancer doubled because of PSA testing and aggressive case finding.

Rationale for screening
- Surgery may be curative for younger men with moderately to poorly differentiated cancer which is confined to the prostate. Screening may be life saving for these patients.


30 Chodak GW, Thisted RA, Gerber GS, et al. Results of conservative management of clinically localized prostate cancer. N Engl J Med 1994;330:242–8. This analysis of six cohorts showed that men (mean age of 70 years) with well to moderately differentiated prostate cancer (Gleason sum of 2–7) had a 10 year disease specific survival of 87% and were five times as likely to die from other causes as from prostate cancer. However, 16% of survivors had metastases by the 10 year mark. Those with poorly differentiated cancer (sum of 8–10) had a disease specific survival of only 34%.
• Watchful waiting may be preferable for older men with well to moderately well differentiated locally confined prostate cancer. The advantage of early detection in this group is not clear.\textsuperscript{30}

• There is a large reservoir of undiagnosed “latent” prostate cancer, much of which would never become clinically apparent without screening.\textsuperscript{31} Screening may be harmful in these cases, since it can lead to unnecessary biopsies and prostatectomies.

**Prostate cancer screening modalities**

• *Digital rectal examination (DRE)*, the original prostate cancer screening test, may identify peripheral lesions.

• *Prostate specific antigen (PSA)* is the most sensitive test for prostate cancer. The threshold for a positive test is commonly set at 4.0 ng/ml. A level above this threshold triples the odds that a man over 50 has a clinically significant (>0.5 ml) tumor that is still intracapsular.\textsuperscript{28}

• *Transrectal ultrasonography (TRUS)* uses biplanar probes to identify suspicious areas of the prostate. This test is currently used mostly to follow up abnormal DRE and PSA results.

**Accuracy of screening modalities**

• In one study of prostate cancer screening, the serum PSA was positive in 15% of subjects.\textsuperscript{32} Of these, 32% had cancer by biopsy (PPV = 32%). DRE was positive in an additional 11%. Of these, 10% had cancer.

• The cancer detection rate for all men screened by PSA was 4.6%. Of these cancers, 89% were well to moderately well differentiated.

• In another study, 10,500 men were screened with PSA, DRE, and TRUS.\textsuperscript{33} If the PSA was >4.0 ng/ml or DRE or TRUS was abnormal, a biopsy was performed. About 21% of screenings led to a biopsy. About 21% of biopsies were positive for cancer, yielding a cancer detection rate of 4.5% of the 10,500 screened men. From this study the following results were obtained.

**Positive Predictive Value by Level of PSA**

<table>
<thead>
<tr>
<th>ng/ml</th>
<th>Cancer detection rate</th>
<th>Patients in category</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0–0.9*</td>
<td>0.1%</td>
<td>21%</td>
</tr>
<tr>
<td>1.0–1.9*</td>
<td>1.3%</td>
<td>41%</td>
</tr>
<tr>
<td>2.0–2.9*</td>
<td>2.2%</td>
<td>16%</td>
</tr>
<tr>
<td>3.0–3.9*</td>
<td>6.3%</td>
<td>9%</td>
</tr>
<tr>
<td>4.0–9.9</td>
<td>21.7%</td>
<td>10%</td>
</tr>
<tr>
<td>&gt; 10.0</td>
<td>52.1%</td>
<td>2%</td>
</tr>
<tr>
<td>Overall</td>
<td>4.5%</td>
<td>100%</td>
</tr>
</tbody>
</table>

* Biopsies were done only if DRE or TRUS were also positive.

• The cancer detection rate was the number of cancers divided by total number of patients in the same PSA category.

• DRE added modestly to PSA results. Of 473 cancers diagnosed in this study, 362 were positive by PSA threshold of

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\textsuperscript{31} Potosky AL, Miller BA, Albertsen PC, Kramer BS. The role of increasing detection in the rising incidence of prostate cancer. *JAMA* 1995;273:348–52. The authors relate an 82% increase in prostate cancer incidence from 1988 to 1991 to the use of PSA screening. Studies have shown that PSA levels naturally increase with age. Whether a higher cutoff (for example, 6.5 ng/ml) should be used in older men is an open question.

\textsuperscript{32} Catalona WJ et al. Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer. *J Urol* 1994;151:1283–90. A study of PSA screening and digital rectal exams (DREs) in 6630 male volunteers over 50 (mean age 63). A PSA ≥ 4.0 micrograms/l was considered positive. The limitation of this study is that many of the cancers detected through screening may have been clinically insignificant. It is not clear whether they were destined to cause morbidity or mortality.

4.0 ng/ml (PPV = 30%). DRE detected an additional 82 cancers that had been missed by PSA but required 639 additional biopsies (PPV = 13%). TRUS picked up an additional 39 cancers but required 436 more biopsies (PPV = 9%).

### Prostate Cancer Detection in 10 500 Men

<table>
<thead>
<tr>
<th>Modality</th>
<th>Biopsies</th>
<th>Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA alone</td>
<td>1192</td>
<td>362</td>
</tr>
<tr>
<td>PSA + DRE</td>
<td>1831</td>
<td>434</td>
</tr>
<tr>
<td>PSA + DRE + TRUS</td>
<td>2267</td>
<td>473</td>
</tr>
</tbody>
</table>

**A natural experiment**

- In a study of 22 000 men over 50 (mean age 64) followed for 10 years in a cancer prevention trial, a selection of baseline serum samples were stored.
- At the end of the trial, the baseline samples were unfrozen and examined for PSA levels, which were then compared to clinical outcomes. The outcomes were not influenced by PSA results.
- About 520 men (2.3%) had developed clinically apparent prostate cancer during the decade, and an estimated 52 (0.23%) died of the disease.
- Baseline PSA levels were > 4.0 micrograms/l in 46% (about 240) of the men who developed prostate cancer and in 9% (about 2000) of healthy controls (LR = 5.1). The positive predictive value was 11%.
- The unanswered question was: In these 22 000 men, how many of the 52 prostate cancer deaths over 10 years could have been prevented by knowledge of the baseline PSA level and, conversely, how many of the estimated 2000 false positives would have led to unnecessary biopsies and prostatectomies?

**Summary and conclusions**

- Serum PSA is the most sensitive screening test for prostate cancer. PSA levels > 4.0 ng/ml are associated with clinically important tumors that are still at a curable stage.
- Serum PSA may be expected to be positive in about 10–12% of asymptomatic patients and yield a 30% cancer rate on biopsy. What proportion of these are clinically important is currently unknown.
- DRE and TRUS add modestly to sensitivity of PSA testing.
- One decision analysis model did not support PSA screening as it may increase morbidity and will raise costs dramatically.35
- Another model suggested that screening may be reasonable in younger men if optimistic assumptions consistent with existing observational data were made.36
- A randomized trial is necessary to provide a definitive answer. At least three large trials are under way.

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34 Gann PH, Hennekens CH, Stampfer MJ. A prospective evaluation of plasma prostate-specific antigen for detection of prostatic cancer. JAMA 1995;273:289–94. The sensitivity of PSA screening increased with more aggressive tumors. The average diagnostic lead time provided by screening was estimated to be 5.5 years.


For now, a decision to do PSA screening should involve the patient’s preference and the weighing of potential benefit and harm.

**Testicular cancer**

*Epidemiology and conclusions*

- In 1999, the estimated number of newly diagnosed testicular cancer cases in the US was 7400 and the estimated number of testicular cancer deaths was 300.1
- Advances in treatment increased the five-year survival rate from 79% in 1975 to 95% in 1994.1
- The exceedingly low mortality rate makes screening unnecessary.
- It is not clear that screening even as many as 100,000 men would save a single life.

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Age group (notes)</th>
<th>Modality</th>
<th>Screenings</th>
<th>Evaluations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>40–49 (1)</td>
<td>Mammography</td>
<td>5000–10,000</td>
<td>80–160 biopsies</td>
</tr>
<tr>
<td></td>
<td>50–74 (2)</td>
<td>Mammography</td>
<td>2000</td>
<td>50 biopsies</td>
</tr>
<tr>
<td></td>
<td>≥75 (3)</td>
<td>Mammography</td>
<td>2000 (est)</td>
<td>50 biopsies (est)</td>
</tr>
<tr>
<td>Cervical</td>
<td>20–75 (4)</td>
<td>PAP test</td>
<td>1800 (est)</td>
<td>Unknown (est)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>≥50 (5)</td>
<td>FOBT (rehydrated)</td>
<td>2800</td>
<td>130 colonoscopies</td>
</tr>
<tr>
<td></td>
<td>≥50 (6)</td>
<td>FOBT (non-rehyd.)</td>
<td>2000</td>
<td>20 colonoscopies</td>
</tr>
<tr>
<td></td>
<td>≥50 (7)</td>
<td>Sigmoidoscopy</td>
<td>300 (est)</td>
<td>100 colonoscopies (est)</td>
</tr>
<tr>
<td>Lung</td>
<td>≥50 (8)</td>
<td>Chest radiograph</td>
<td>Ineffective</td>
<td>Not applicable</td>
</tr>
<tr>
<td></td>
<td>≥50 (8)</td>
<td>Sputum cytology</td>
<td>Ineffective</td>
<td>Not applicable</td>
</tr>
<tr>
<td></td>
<td>≥50 (9)</td>
<td>Helical CT</td>
<td>70–300 (est)</td>
<td>2–10 biopsies (est)</td>
</tr>
<tr>
<td>Ovarian</td>
<td>≥40 (10)</td>
<td>Transvaginal US</td>
<td>5000–20,000 (est)</td>
<td>30–120 laparotomies (est)</td>
</tr>
<tr>
<td>Prostate</td>
<td>≥50 (11)</td>
<td>Serum PSA</td>
<td>850–4400 (est)</td>
<td>80–400 biopsies (est)</td>
</tr>
</tbody>
</table>

Each row represents total effort to prevent a cancer death by the screening modality identified. (for example, it takes 2000 FOBTs and 20 colonoscopies to prevent a colorectal cancer death)

(est) = estimated (i.e. not determined by a randomized trial)

**Assumptions:**
1. 1 life is saved for every 5000–10,000 mammograms (ref. 12) – proven; and 16 biopsies are performed for every 1000 mammograms (ref. 3) – proven.
2. 1 life is saved for every 2000 mammograms (ref. 6 and 7) – proven; and 25 biopsies are performed for every 1000 mammograms (ref. 3) – proven.
3. Effectiveness is equal to that seen in women aged 50–74 – unproven.
4. Effectiveness is 105 lives saved in 10,000 women over 18 screenings (ref. 15) – supported by observation.
5. Data from randomized trial (ref. 19).
6. Data from randomized trial (ref. 21).
7. Effectiveness is 60% reduction in colorectal cancer mortality (ref. 22) – supported by observation.
8. Data from randomized trial (ref. 23).
9. 10–50% of cancers detected will represent saved lives (ref. 24) – unproven.
10. 10–50% of cancers detected will represent saved lives (ref. 26) – unproven.
11. Effectiveness is 10–50% reduction in prostate cancer mortality over 10 years (ref. 34) – unproven (From reference 34: screening 22,000 men yielded 2000 positive PSAs; there were 52 prostate cancer deaths over 10 years).
## Epidemiology
### Incidence and sequelae
- Stroke is the third leading cause of death in the US.1
- There are 500,000 strokes per year in the US with 150,000 deaths.1
- Twenty percent of strokes are hemorrhagic (subarachnoid 8%, intracerebral 12%) and 80% are ischemic.
- Among ischemic strokes, 17% are atherosclerotic (9% extracranial and 8% intracranial), 30% lacunar, 21% cardioembolic, 31% cryptogenic, and 1% other.2
- Mortality rates at 30 days, one year, and five years after ischemic stroke are 8%, 21%, and 44%, respectively.3

### Risk factors
#### Unmodifiable risk factors
- Male sex
- Older age
- Race: African-Americans and Hispanic-Americans are at greater risk than white Americans.

#### Atherosclerotic risk factors
- Hypertension: a contributing factor in 70% of stroke patients.1
- Lipids: there is controversy concerning whether or not baseline cholesterol affects the risk of stroke, even though HMG Co-A reductase inhibitors have been proven to reduce risk.4
- Smoking5
- Alcohol consumption6
- Diabetes: better glycemic control has not yet been proven to reduce risk of stroke.

#### Previous cerebrovascular events
- Transient ischemic attack (TIA): after TIA 33% of patients eventually have a completed stroke; of these, 20% in the first month and 50% in the first year. After 5–10 years the risk returns to that of the general population.7
- Completed stroke: subsequent stroke rate is 5–9% per year.8

#### Cardiac disease as a risk factor for embolic stroke
- Major risk: atrial fibrillation, mechanical valve, dilated cardiomyopathy, recent MI, left ventricular hypertrophy, enlarged left atrium, intracardiac thrombus.
- Minor risk: mitral valve prolapse, severe mitral annular calcification, patent foramen ovale, atrial septal aneurysm.

---


### Relative Risk of Stroke

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>1.2</td>
</tr>
<tr>
<td>African Amer. v whites</td>
<td>2.4</td>
</tr>
<tr>
<td>Latin Amer. v whites</td>
<td>2.0</td>
</tr>
<tr>
<td>Total cholesterol: increase</td>
<td>1.4</td>
</tr>
<tr>
<td>40 mg/dl, patients &lt; 45</td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td></td>
</tr>
<tr>
<td>&lt; 10/d</td>
<td>1.5</td>
</tr>
<tr>
<td>10–20/d</td>
<td>1.8</td>
</tr>
<tr>
<td>&gt; 20/d</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Continued
Asymptomatic carotid disease

- Carotid stenosis $\geq 75\%$ is associated with a yearly risk of 2.5% for ipsilateral stroke and of 6.5% for fatal MI.
- For stenosis $< 75\%$, the risk of stroke is $< 1\%/\text{year}$.
- Other risk factors include thrombophilia, collagen vascular disease, and cocaine use.

Diagnosis

Classification by symptoms

**Transient ischemic attack**
- Focal deficit of abrupt onset (maximal symptoms in $< 5$ minutes).
- Most last 2–25 minutes but always resolve within 24 hours.
- Usually due to embolism from a carotid artery or the heart, occasionally from intracranial arteries. The differential diagnosis includes aneurysmal leak, seizure, syncope, hypoglycemia, and migraine.

**Minor stroke**
- Complete recovery after 24 hours or persistent non-disabling neurologic deficits.

**Completed stroke**
- Focal cerebral dysfunction that stabilizes and may improve but has not completely resolved by three weeks.

By cerebrovascular territory

Anatomy is important (see criteria at right). Neuroimaging does not always identify the site of the stroke and distinction between lacunar, anterior infarction, and posterior disease will help determine the need for carotid duplex and echocardiogram.

Lacunar syndromes

- Lacunar infarcts (LACI)
  - May be clinically silent.
  - Caused by occlusion of penetrating branches of major cerebral arteries by miniature atherosclerotic plaques or lipohyalinosis.
  - Strongly associated with hypertension and diabetes.
  - Usually subcortical

Carotid artery disease

- Total anterior circulation infarcts (TACI)
- Partial anterior circulation infarcts (PACI)

Vertebrobasilar arterial disease

- Posterior circulation infarcts (POCI)
- The Banford article does not include vertigo as a criterion. Vertigo is a common symptom of vertebrobasilar insufficiency.
- Isolated vertigo, dizziness, syncope, or nausea are seldom caused by TIAs. Patients may have episodes of transient vertigo, but they will usually have different neurologic symptoms at other times.

---

**Ex-smoker v non-smoker** 1.2
**Alcoholic drinks/week:**
- for ischemic stroke: $\geq 21^1$
- for hemorrhagic stroke: 2.0–4.0
- for ischemic stroke: 0.8
- for hemorrhagic stroke: 0.9
- Diabetes $^1$
  - for ischemic stroke: 1.8
  - for all strokes: 3.0
- Rise in DBP by 10 mmHg $^4$ 1.8

**Stroke syndromes:**

**Lacunar infarcts (LACI)**
- Patients usually have one of the following,
  - pure motor stroke
  - pure sensory stroke
  - sensory-motor stroke
  - ataxic hemiparesis

**Total anterior circulation infarcts (TACI)**
- Patients present with all three of the following sets of symptoms.
  - New higher cerebral dysfunction (dysphagia, dyscalculia, visual-spatial disorder) or impairment of consciousness
  - Homonymous hemianopia
  - Hemiparesis and/or hemisensory deficit of at least two of the following three areas: face, arm, leg

**Partial anterior circulation infarcts (PACI)**
- May present with any of the following.
  - Two of the three criteria for TACI
  - Higher cerebral dysfunction alone
  - A more restricted sensory/motor component than TACI (for example, confined to one limb or to the face and hand but not the whole arm)

**Posterior circulation infarcts (POCI)**
- Presents with any of the following.
  - Ipsilateral cranial nerve palsy with contralateral motor and/or sensory deficit
  - Bilateral motor and/or sensory deficit
  - Disorder of conjugate eye movement
  - Cerebellar dysfunction without ipsilateral long tract deficit (i.e. ataxic hemiparesis)
  - Isolated homonymous hemianopia

Vertebrobasilar occlusion occurs about 25% as often as carotid artery occlusion.\(^9\)

The mortality rate is 75–86%.

Up to 50% of patients present with coma, due to involvement of the reticular activating system.\(^9\)

### Sensitivity and Specificity of Clinical Criteria for Ischemic Stroke Syndromes\(^{10}\)

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TACI</td>
<td>43</td>
<td>96</td>
</tr>
<tr>
<td>PACI</td>
<td>72</td>
<td>76</td>
</tr>
<tr>
<td>LACI</td>
<td>70</td>
<td>93</td>
</tr>
<tr>
<td>POCI</td>
<td>70</td>
<td>96</td>
</tr>
</tbody>
</table>

### By etiology

**Intracerebral hemorrhage**

- Massive hemorrhage presents with sudden onset of severe headache and rapid deterioration of consciousness. These symptoms may not be present in the setting of smaller peripheral hemorrhages.\(^{11}\)
- There is usually no history of previous TIA.

**Cardioembolic**

- Characterized by different symptoms during recurrent cerebrovascular events due to embolic compromise of different vascular territories. Symptoms are maximal from the onset of the event.

**Ischemic**

- May be difficult to distinguish from the other hemorrhagic types.
- With recurrent events (i.e. TIAs), symptoms will be similar.

### Physical examination

- Detailed neurologic exam
- Cardiac: assess for arrhythmia, murmurs, gallops, or displaced PMI.
- Blood pressure
- Evidence of peripheral embolism: blue toes, unilateral cyanosis of a limb, flank tenderness.
- Ocular hemorrhage or nuchal rigidity suggests intracranial hemorrhage.

### Diagnostic testing

**Electrocardiogram**

Stroke can occur with acute MI or arrhythmia.

**Blood tests**

- A complete blood count and PT/PTT should be done to screen for polycythemia vera, thrombocytosis, and thrombophilia.
Serum electrolytes can reveal uremia or hypoglycemia as a cause of neurologic symptoms.

Consider VDRL and ESR to screen for vasculitis.

Consider a detailed thrombophilia work up if no obvious cause for symptoms is found.

Consider screening for cocaine use.

**Non-contrast head CT**

- For suspected TIA, obtain a CT scan of the head to rule out subdural hematoma or brain tumor that may rarely present with TIA-like symptoms. CT reveals brain infarction in area corresponding to TIA symptoms 29–34% of the time.\(^\text{12}\)
- For suspected acute stroke, a CT should be performed at once to distinguish hemorrhagic from non-hemorrhagic stroke and to detect non-vascular lesions (tumors). The distinction is crucial because the work up and treatment differ greatly. Early CT may miss signs of infarctions, even large ones, but a lack of blood supports the diagnosis of ischemic stroke and permits treatment with antiplatelet agents and anticoagulants. By seven days, 100% of the infarcts that will ever be revealed by CT will have appeared.

**MRI**

- Detects ischemia earlier than CT, but has less clear resolution of intracerebral hemorrhage.\(^\text{12}\) CT should be done first because it is more important to quickly rule out hemorrhage than to definitively diagnose an infarct.

**Evaluation of suspected ischemic disease**

**Carotid duplex ultrasound**

- Combines real time B-mode ultrasound with carotid Doppler.
- It may be better than angiography in detecting plaques and ulcers and can distinguish high grade stenosis from occlusion.\(^\text{13}\)
- **Indications:** for evaluation of patients with unilateral anterior neurologic symptoms or signs to determine if they might benefit from carotid endarterectomy or possibly anticoagulation.

**Carotid Doppler**

- Less expensive than duplex ultrasound, but some studies report lower sensitivity.\(^\text{13}\)

**Transcranial Doppler**

- Evaluates large intracranial vessels, the posterior circulation, and the degree of carotid stenosis.
- No proven role in the clinical management of patients with stroke or TIA.

**Magnetic resonance angiography (MRA)**

- Visualizes both the extra- and intracranial circulations.\(^\text{13}\)

---


Diffusion weighted MRI may distinguish new from old strokes.

Cannot distinguish occlusion from high grade stenosis and it overestimates degree of stenosis.

Is as sensitive as duplex ultrasound for detecting extracranial carotid stenosis, but is more expensive.

**Intra-arterial digital subtraction angiography**
- Evaluates extracranial and intracranial vessels and assesses intimal surfaces.
- Provides similar results as conventional angiography, with less expense, lower contrast dose, and a smaller catheter with less potential for local injury.
- Potential complications include peripheral vascular and cerebrovascular events. Rates vary according to center for these complications. In the Asymptomatic Carotid Atherosclerosis Study, 0.7% of patients had an ischemic stroke caused by cerebral angiogram.14

**Indications for intra-arterial digital subtraction angiography**
- Before endarterectomy to confirm the degree of stenosis because of the false positive rate of non-invasive tests.12
- If long term anticoagulation for severe vertebrobasilar or intracranial disease is being considered.
- Consider in patients with a high pretest probability of extracranial carotid disease and negative ultrasound.

**Evaluation of suspected embolic disease**

**Transthoracic echocardiography (TTE)**
- Should be reserved for young patients, patients with heart disease, cardiac risk factors, cardiac symptoms, or EKG abnormalities.15
- Is probably not useful in patients with lacunar syndromes.
- It is not cost effective to perform TTE on all patients with TIA or stroke because of the low prevalence of findings.

**Transesophageal echocardiography (TEE)**
- More sensitive and specific than TTE for atrial and aortic sources of emboli. It should be used if no source is found and clinical suspicion for embolization is high.

**Yield of Echocardiography after Stroke**16

<table>
<thead>
<tr>
<th></th>
<th>All patients (%)</th>
<th>Patients with cardiac disease (%)</th>
<th>Patients without cardiac disease (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTE</td>
<td>4</td>
<td>13</td>
<td>0.7</td>
</tr>
<tr>
<td>TEE</td>
<td>11</td>
<td>19</td>
<td>1.6</td>
</tr>
</tbody>
</table>

(Percent of patients with thrombus, vegetation, or tumor detected by transthoracic (TTE) and transesophageal (TEE) echocardiogram)

**Holter monitoring**
- Is only useful to evaluate patients with a previous history of atrial fibrillation (AF) or symptoms suggestive of arrhythmia.
- May be used when no source is found after other tests are done.15

Symptomatic patients with occlusion seen on non-invasive testing should undergo angiography because they may actually have a tight stenosis and benefit from endarterectomy.

MRA may be of benefit in imaging the vertebrobasilar system, but it is not clear that this knowledge will effectively alter management or outcome.


**Meta-analysis of 70 Studies. For Patients with 70% Stenosis**

<table>
<thead>
<tr>
<th></th>
<th>Sens (%)</th>
<th>Spec (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duplex ultrasound</td>
<td>88</td>
<td>92</td>
</tr>
<tr>
<td>Doppler ultrasound</td>
<td>86</td>
<td>94</td>
</tr>
<tr>
<td>MRA</td>
<td>92</td>
<td>88</td>
</tr>
</tbody>
</table>

15 Come PC, Riley MF, Bicas NK. Roles of echo and arrhythmia monitoring in the evaluation of patients with suspected systemic embolism. Ann Neurol 1983;13: 527–31. In patients with symptoms suggesting embolism, echocardiography found cardiac diseases known to be associated with thrombus formation in 33%. Excluding patients without risk of heart disease would eliminate 38% of echos without missing any lesions. Of 150 patients who underwent Holter monitoring, the test did not detect atrial fibrillation (AF) in any patient who did not already have EKG evidence of AF on admission or a previous history of AF.12


Other TEE findings associated with “cryptogenic stroke” include aortic arch atheroma, patent foramen ovale, atrial septal aneurysm, and spontaneous echo contrast.
Treatment

Risk factor modification

*Primary prevention*\(^{17}\)
- Prevention of first stroke by risk factor modification has only been proven in clinical trials for blood pressure reduction and treatment of hypercholesterolemia after MI.
- Modification of other risk factors is assumed to be of benefit because of strong association of these factors with stroke seen in observational studies.

*Secondary and tertiary prevention*\(^{17}\)
- Prevention of stroke after TIA or of stroke recurrence by modification of risk factors has not yet been proven in any clinical trial.
- As in primary prevention, modification of risk factors is assumed to be of benefit because of strong epidemiologic association of these factors with stroke in observational studies.

- **Smoking cessation**
- **Reduction or cessation of alcohol consumption**
- **Diabetes:**
  - Large, well designed trials have so far failed to show a reduction in macrovascular events with tight glycemic control.
- **Hypertension:**
  - Reduction of diastolic BP by 5 points in patients with a diastolic BP <105 produced a RRR of 38% for fatal stroke and 11% for total deaths in patients without previous CVA.\(^{18}\)
  - In patients over 60, the ARR for a first stroke with antihypertensive therapy is 1.2% over five years. The ARR for death from stroke is 0.8%.\(^{19}\)
- **Cholesterol:**
  - There is not a clear and strong association between cholesterol and risk of stroke in observational studies.
  - In two trials, treatment with pravastatin 40 mg/dl following MI resulted in reductions in stroke (a secondary endpoint). Of note, both groups defined stroke as any cerebrovascular event lasting >24 hours, and did not quantify outcomes in terms of irreversible events.\(^{20,21}\)

| Reduction of Stroke with HMG-CoA Reductase Inhibitors\(^{20,21}\) |
|------------------|--------|--------|
| **Trial**        | **RRR (%)** | **ARR (%)** |
| CARE (five years) | 30     | 1.1    |
| LIPID (6 years)   | 19     | 0.8    |

*Antiplatelet therapy*
- A meta-analysis of antiplatelet trials showed an ARR of 2.2% for non-fatal stroke after TIA or prior stroke for patients treated with antiplatelet therapy. The ARR for...

---


non-fatal MI was 1% and the ARR for stroke, MI, or vascular death was 3.8%.\textsuperscript{22}

\textit{Aspirin}
- Often considered first line antiplatelet therapy because of its low cost. However, when the costs of stroke treatment, MI treatment, and rehabilitation are taken into account aspirin and dipyridamole in combination are more cost effective.
- The value of aspirin in lacunar infarcts and severe strokes is unknown, but its use is reasonable.
- Although aspirin has been reported to be less effective in women, this is probably related to the small number of women studied and the lower event rate in women.

\textbf{Aspirin (75 mg) v Placebo: Secondary Prevention after TIA or Stroke}\textsuperscript{23}

<table>
<thead>
<tr>
<th></th>
<th>Non-fatal stroke (%)</th>
<th>Non-fatal MI (%)</th>
<th>Death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>11.4</td>
<td>5.3</td>
<td>9.0</td>
</tr>
<tr>
<td>Placebo</td>
<td>14.9</td>
<td>5.8</td>
<td>10.1</td>
</tr>
</tbody>
</table>

\textit{Dipyridamole}
- 50mg of aspirin plus 400mg of sustained release dipyridamole reduced the rate of stroke and death compared with placebo or aspirin or dipyridamole alone.

\textbf{Dipyridamole and Aspirin in the Secondary Prevention of Stroke}\textsuperscript{24}

\begin{tabular}{lll}
 & Completed stroke (%) & Death (%) \\
Aspirin & 12.5 & 11.0 \\
Dipyridamole & 12.8 & 11.4 \\
Dipyridamole + aspirin & 9.5 & 11.2 \\
Placebo & 15.0 & 12.2 \\
\end{tabular}

\textit{Ticlopidine}
- Patients who cannot tolerate aspirin, who have neurologic symptoms on aspirin, or who have had a major stroke may be considered for ticlopidine.
- It is slightly more effective than aspirin, with an ARR for stroke of about 1% per year in patients with a history of TIA.
- Side effects include neutropenia (2.4%). A complete blood count should be checked every two weeks for the first three months of use. Rash and diarrhea (12%) are also frequent.\textsuperscript{5,15}

\textbf{Ticlopidine in the Secondary Prevention of Stroke}\textsuperscript{25}

<table>
<thead>
<tr>
<th></th>
<th>Stroke at 3 years (%)</th>
<th>Absolute neutropenia%*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>10</td>
<td>0.85</td>
</tr>
</tbody>
</table>

\*All episodes of absolute neutropenia (neutrophil count <450/mm\textsuperscript{3}) occurred 1–3 months after starting therapy and resolved within several weeks of stopping therapy.


\textsuperscript{23} SALT Collaborative Group. Swedish Aspirin Low-Dose Trial (SALT) of 75mg aspirin as secondary prophylaxis after cerebrovascular ischaemic events. Lancet 1991;338:1345–9.

\textsuperscript{24} Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Louwenthal A. European Stroke Prevention Study 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J Neurol Sci 1996;143:1–13. RCT of 6602 patients with a history of stroke or TIA during the previous three months. This combination should not be used if ASA is not tolerated at higher doses or in ASA failures.

\begin{tabular}{lll}
\textbf{Costs of Antiplatelet Therapy} & \textbf{Cost per\hspace{1em}patient\hspace{1em}year} & \textbf{Lifetime\hspace{1em}cost/patient} \\
Aspirin & $ 7 & $44396 \\
Clopidogrel & $873 & $50388 \\
Aspirin and dipyridamole & $218 & $41425 \\
\end{tabular}

Association with neutropenia has led many practitioners toward clopidogrel as the second line agent.

**Clopidogrel**
- It provides a small reduction in the combined outcomes of stroke, MI, and other vascular deaths, compared to aspirin in patients with a history of TIA or stroke.
- It has fewer side effects than aspirin and it is not associated with neutropenia as is ticlopidine.
- It is much more expensive than aspirin.

**Clopidogrel in Secondary Prevention of Stroke**

<table>
<thead>
<tr>
<th>Stroke/patient year (%)</th>
<th>Stroke, MI or other vascular death/patient year (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin 5.6</td>
<td>7.71</td>
</tr>
<tr>
<td>Clopidogrel 5.2</td>
<td>7.15</td>
</tr>
</tbody>
</table>

**Anticoagulation**
- There are no data to support the use of warfarin for preventing non-cardioembolic cerebral ischemic events.
- Warfarin is sometimes used in patients who have events or side effects on antiplatelet agents, but should be used only after clopidogrel fails.
- Warfarin has also been recommended for patients with high grade intracranial stenosis or severe, symptomatic, inoperable carotid or vertebrabasilar stenosis. In such cases, warfarin is usually given for 3–6 months and then switched to aspirin. There are no well designed trials to support this recommendation.
- Trials of the use of warfarin after ischemic stroke or TIA have not been impressive.

**ACCP recommendations for prevention of stroke recurrence with antiplatelet agents**
- All patients without contraindication should receive an antiplatelet agent after a non-cardioembolic cerebral ischemic event (atherothrombotic, lacunar, or cryptogenic).
- Options for initial therapy:
  - aspirin 50–325 mg qd
  - aspirin/dipyridamole ER 25/200 mg
  - clopidogrel 75 mg qd.
- Aspirin plus dipyridamole is more effective than aspirin alone and may be more effective than clopidogrel.
- Inadequate data are available to conclude for or against warfarin in non-cardioembolic stroke when dosing to a target INR <3. At INRs of 3–4.5 the risk of brain hemorrhage outweighs benefit.
Surgical management
Symptomatic carotid stenosis
Carotid endarterectomy (CEA)
- Recommended for patients with TIAs or a non-disabling stroke in the distribution of the carotid arteries and a >70% stenosis of the external carotid. Not indicated in lacunar disease.
- Endarterectomy is clearly not indicated in symptomatic patients with mild stenosis.
- For symptomatic patients with moderate stenosis, there are substantial risks and benefits that should be discussed with the patient.
- CEA should only be performed at an institution where the total perioperative stroke and death rate is lower than 6%.14 In most hospitals the low complication rate seen in studies cannot be duplicated; the average rate of perioperative stroke and death in the community is 10%.29

Carotid angioplasty
- Has been performed but is high risk; its efficacy has not been established.29

Asymptomatic carotid stenosis
Carotid endarterectomy
- Controversial in asymptomatic patients. For patients with asymptomatic stenosis >60%, CEA may confer a significant decrease in stroke risk, as long as the perioperative risk of stroke or death is <3% at the patient’s hospital.

ARR and Number Needed to Treat (NNT) for All Strokes Following Carotid Endarterectomy

<table>
<thead>
<tr>
<th>Study (follow up)</th>
<th>Degree of stenosis*</th>
<th>Presence of symptoms</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>NASCET (2 yrs)30</td>
<td>Severe</td>
<td>Yes</td>
<td>15.0%</td>
<td>7</td>
</tr>
<tr>
<td>ECST (3 yrs)31</td>
<td>Severe</td>
<td>Yes</td>
<td>9.6%</td>
<td>10</td>
</tr>
<tr>
<td>NASCET (5 yrs)32</td>
<td>Moderate</td>
<td>Yes</td>
<td>8.4%</td>
<td>12</td>
</tr>
<tr>
<td>ECST (6 yr)33</td>
<td>Moderate</td>
<td>Yes</td>
<td>-6.4%</td>
<td>-</td>
</tr>
<tr>
<td>NASCET (5 yrs)32</td>
<td>Mild</td>
<td>Yes</td>
<td>-4.3%</td>
<td>-</td>
</tr>
<tr>
<td>ECST (6 yr)33</td>
<td>Mild</td>
<td>Yes</td>
<td>0.5%</td>
<td>-</td>
</tr>
<tr>
<td>VA Trial (4 yrs)34</td>
<td>Severe</td>
<td>No</td>
<td>3.9%</td>
<td>26</td>
</tr>
<tr>
<td>ACAS (5 yrs)35</td>
<td>Severe</td>
<td>No</td>
<td>5.1%</td>
<td>20</td>
</tr>
</tbody>
</table>

*Severe stenosis was >70% stenosis. Moderate stenosis was 30 (or 50)-70% stenosis.

Vertebrobasilar disease
- Vertebrobasilar angioplasty has been performed, but is high risk; its efficacy has not yet been established.9
- Surgery for vertebobasilar disease is reserved for patients refractory to maximal medical treatment. There are no well designed trials assessing its benefit.9

Notes on the randomized trials of carotid endarterectomy
- The control groups were treated with antiplatelet therapy.
- Great efforts were made to minimize the risks of surgery. Hence, these results are generalizable only to centers with perioperative stroke and death rates <3–6%.
- Inclusion required non-disabling stroke or TIA in the carotid territory within the previous 3–6 months.
- In all of these studies there was a high death rate in both groups, often due to cardiac disease. Poor health status and comorbid conditions argue against a decision to operate.

31 European Carotid Surgery Trialists’ Collaborative Group. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70–99%) or with mild (0–29%) carotid stenosis. Lancet 1991;337:1235–42.
Hospital admission: indications

- Acute stroke: all patients
- Transient ischemic attack\(^{36}\)
  - Ongoing episodes
  - Severe deficits
  - >4 episodes in the past two weeks
  - Increasing frequency, severity, or duration of symptoms
  - Probable cardiac source
  - If a single episode of symptoms occurred more than several days before evaluation or if it involved only transient monocular blindness, an expedited outpatient work up can be performed.

During CEA, patients are under general anesthesia for two hours, with the artery occluded for 30 minutes. The procedure can be done with the patient awake, but there is no change in risk. The patient can go home in 24–48 hours. The risk of ipsilateral stroke after CEA done for TIA is 1–2% per year; when done for stroke it is 2–3% per year.\(^{6}\)


### Table 9.1  Agents for cerebrovascular disease.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage forms</th>
<th>Usual dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>81/325 mg</td>
<td>81–325 mg PO qd</td>
<td></td>
</tr>
<tr>
<td>Dipyridamole (Persantine)</td>
<td>25/50/75 mg</td>
<td>75 mg PO qid</td>
<td></td>
</tr>
<tr>
<td>Ticlopidine (Ticlid)</td>
<td>250 mg</td>
<td>250 mg PO bid</td>
<td></td>
</tr>
<tr>
<td>Aspirin/dipyridamole ER (Aggrenox)</td>
<td>25/200 mg</td>
<td>1 tab PO bid</td>
<td>Check CBC for neutropenia q two weeks for the first three months</td>
</tr>
<tr>
<td>Clopidogrel (Plavix)</td>
<td>75 mg</td>
<td>75 mg PO qd</td>
<td></td>
</tr>
</tbody>
</table>
10 Coronary artery disease
Nate Link and William Slater

Epidemiology
Incidence and prevalence
- Coronary artery disease (CAD) is the leading cause of death in Americans, accounting for about 500,000 deaths each year. The annual incidence of MI is about 1.5 million.
- Up to 2 million middle aged men may have silent myocardial ischemia.1

Risk factors
- Lipid levels: low HDL (<35 mg/dl) and high LDL are independently associated with CAD (HDL especially in women).
- Diabetes: increased risk is related to hyperglycemia and hyperinsulinemia, both of which are atherogenic.
- Hypertension: systolic and diastolic blood pressure are independent risk factors but systolic is the preferred marker.
- Smoking: promotes atherogenesis, ischemia, and thrombogenesis. Risk mostly disappears within three years after cessation.
- Family history: especially premature disease (parent with MI before 60), but it is difficult to quantify the independent effect.
- Left ventricular hypertrophy: a powerful independent risk factor for CAD (more so than DM or smoking).
- Homocysteine: observational studies demonstrate that higher levels are associated with a 20–40% increased risk of cardiovascular events.2 Nine randomized trials to evaluate the effect of treating high homocysteine are currently under way.
- C-reactive protein: observational studies demonstrate that the prevalence of CAD is increased by 50% for each doubling of the CRP level.3 The pathophysiologic significance of this relationship remains unclear although aspirin and statin drugs could possibly exert their benefit by decreasing coronary artery inflammation.
- Other risk factors: obesity,4 high levels of uric acid, tri-glycerides,5 lipoprotein(a), t-PA antigen, fibrinogen, and leukocytes.
- Protective factors: Include exercise (?causal), moderate EtOH use (1–2 drinks per day), and high HDL (>60).

Diagnosis
Overview of strategy
1. Assess pretest probability of CAD by history, PE, and labs.
2. Perform non-invasive testing if indicated.
3. Perform cardiac catheterization if indicated.
4. Initiate treatment accordingly.


Multivariate risk. A 50 y.o. healthy male has a 10-year risk of CAD of 6%. His risk would increase incrementally to the following levels by adding risk factors in sequence: smoking 9%, diabetes 13%, hypertension (165/90) 21%, and hypercholesterolemia 27%. Calculated using the excellent risk factor formula presented in Anderson KM, Wilson PW, Odell PM, Kannel WB. An updated coronary risk profile. Circulation 1991;83:337–70.


4 Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease. Circulation 1983;67:968–78. The effect of obesity is diminished but still present after adjusting for lipids, hypertension, and glucose tolerance.

5 Wilson PW. Established risk factors and coronary artery disease: the Framingham Study. American Journal of Hypertension 1994;7:7S–12S. A good brief overview of risk factors. States that triglyceride (TG) levels add little after adjusting for HDL levels. Other studies, however, show that TG levels are independent risk factors for MI (but not for angina).

The decision to catheterize should be based on post-test probability, evidence of high risk features, and severity and stability of symptoms (see below).
Clinical assessment

History
- Demographics – age, gender (see table below). Note the decreasing importance of gender with advancing age.
- Description of symptoms (see table below). Classic angina is substernal chest pressure occurring predictably with exertion and relieved within a few minutes by rest.
- Associated risk factors – diabetes, hypertension, family history, hyperlipidemia, lipids, smoking, and menopausal status all modify the probability of disease (see page 91).

Physical exam and laboratory tests
- Physical assessment for risk factors should include blood pressure (for hypertension), fundoscopic exam (for diabetes and hypertension), and cardiac exam (for left ventricular hypertrophy and heart failure).
- Physical assessment for associated conditions should include peripheral vascular exam (for peripheral vascular disease) and neurological exam (for cerebrovascular disease).
- Fasting lipid profile and glucose or glycosylated hemoglobin
- Electrocardiogram for left ventricular hypertrophy, ST-T changes, abnormal conduction, or old myocardial infarction

Using clinical factors to assess the probability of CAD
The table below shows the prevalence of CAD based on age, gender, and quality of symptoms. For this purpose, the three features of angina are 1) substernal location, 2) precipitation by exertion, 3) relief by rest or nitroglycerin. The presence of all three features = typical angina, 2 = atypical angina, and 1 = non-anginal chest pain.

Prevalence of CAD by Age, Gender, and Symptoms

<table>
<thead>
<tr>
<th>Age</th>
<th>Men (1)</th>
<th>Women (1)</th>
<th>Men (2)</th>
<th>Women (2)</th>
<th>Men (3)</th>
<th>Women (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30–39</td>
<td>.05</td>
<td>.01</td>
<td>.22</td>
<td>.04</td>
<td>.70</td>
<td>.26</td>
</tr>
<tr>
<td>40–49</td>
<td>.14</td>
<td>.03</td>
<td>.46</td>
<td>.13</td>
<td>.87</td>
<td>.55</td>
</tr>
<tr>
<td>50–59</td>
<td>.22</td>
<td>.08</td>
<td>.59</td>
<td>.32</td>
<td>.92</td>
<td>.79</td>
</tr>
<tr>
<td>60–69</td>
<td>.28</td>
<td>.19</td>
<td>.67</td>
<td>.54</td>
<td>.94</td>
<td>.91</td>
</tr>
</tbody>
</table>

Exercise stress testing (EST)

Introduction
- Exercise stress testing assists in diagnosis of CAD and in risk stratification of patients already diagnosed with CAD.
- Options for EST include treadmill ECG test (“plain” EST), stress myocardial perfusion imaging (for example, nuclear EST), dipyridamole myocardial perfusion imaging (for example, persantine-thallium test), and stress or dobutamine echocardiography.
- The treadmill ECG test is a standard diagnostic tool that is appropriate in the majority of patients with CAD.
Operating characteristics of the treadmill ECG test

- A positive result is usually defined as non-upsloping ST segment depressions of 1 mm or greater. Sensitivity is about 65–70% and specificity is about 80–85% (LR = 4.3). In general, the more severe the disease, the higher the sensitivity. For left main disease, the sensitivity probably exceeds 90%.
- The probability of disease is further influenced by the exact amount of ST depression as indicated below.

Probability that CAD and Healthy Patients will Achieve Given Levels of ST Segment Depression on a Treadmill ECG Test

<table>
<thead>
<tr>
<th>ST depression in millimeters</th>
<th>CAD patients</th>
<th>Healthy patients</th>
<th>Likelihood ratio (LR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0–0.5</td>
<td>.14</td>
<td>.63</td>
<td>0.2</td>
</tr>
<tr>
<td>0.5–1.0</td>
<td>.21</td>
<td>.23</td>
<td>0.9</td>
</tr>
<tr>
<td>1.0–1.5</td>
<td>.23</td>
<td>.11</td>
<td>2.1</td>
</tr>
<tr>
<td>1.5–2.0</td>
<td>.09</td>
<td>.02</td>
<td>4.5</td>
</tr>
<tr>
<td>2.0–2.5</td>
<td>.13</td>
<td>.01</td>
<td>13</td>
</tr>
<tr>
<td>≥2.5</td>
<td>.20</td>
<td>.005</td>
<td>39</td>
</tr>
</tbody>
</table>

Rules of thumb in treadmill ECG test interpretation

- The treadmill ECG test is a useful yet imperfect diagnostic test for CAD. The high number of false results can be misleading.
- The test is least useful as a diagnostic tool when the physician is fairly certain of the presence or absence of disease. It is most helpful when the pretest probability approaches 50%.
- Interpretation of the test result should take into account the degree of ST segment depression. Greater degrees of ST depression make the diagnosis more likely.
- For diagnostic purposes, sensitivity is increased by discontinuing antianginal meds for 24–48 hours before the test (ASA should be continued). For assessment of medical management, it may be preferable to perform the test while patient is on full medications.

Examples of Pre- and Post-Test Probabilities

<table>
<thead>
<tr>
<th>Patient</th>
<th>Pretest probability</th>
<th>Result (ST)</th>
<th>Post-test probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 38 y.o. woman with atypical angina</td>
<td>.04</td>
<td>0.0 mm</td>
<td>.01</td>
</tr>
<tr>
<td>A 48 y.o. man with atypical angina</td>
<td>.52</td>
<td>1.5 mm</td>
<td>.17</td>
</tr>
<tr>
<td>A 58 y.o. old man with typical angina</td>
<td>.92</td>
<td>1.5 mm</td>
<td>.98</td>
</tr>
<tr>
<td>A 68 y.o. woman with typical angina</td>
<td>.94</td>
<td>1.5 mm</td>
<td>.99</td>
</tr>
</tbody>
</table>

7 Adapted from the Diamond and Forrester article cited above. The LR may be interpreted as the probability that a diseased patient will have a result in the indicated range divided by the probability that a healthy patient will have a result in that range. Thus, CAD patients are about one-fifth (0.2) as likely as healthy patients to have ST depressions in the range of 0–0.5 mm but 39 times as likely as healthy patients to have ST depressions greater than 2.5 mm. Achieving a high rate-pressure product increases the sensitivity of the EST and therefore improves the predictive value of a negative result because high workloads help prevent false negatives. Conversely, achieving a lower workload increases the specificity of the test and improves the predictive value of a positive result (fewer false positives). A reasonable goal is to aim for 85% of the target heart rate. A negative stress test is associated with a good prognosis, even if it is a false negative result. An improvement in EST by use of medications may also have positive prognostic value.

For diagnosis: A result of 1.5 mm ST depression in the 38 y.o. woman still leaves her with a diagnostic probability of only 16%, and a fully negative result in the 58 y.o. man still leaves him with a post-test probability of 70%. In neither case would the EST produce a change in the preclinical assessment, although some physicians would perform an EST in the second patient for prognostic purposes. Note that the 68 y.o. woman has about the same pretest probability as the 58 y.o. man.

For prognosis: The average man >55 with stable angina has a four-year survival rate of 94%. If he does poorly on his EST, his survival rate becomes 81%. If he does well, it increases to 98%.
Myocardial perfusion imaging (e.g. thallium EST)
- Increases EST accuracy and cost.
- Assesses patients with left bundle branch block (LBBB) or otherwise uninterpretable ECGs.
- Increases sensitivity in patients unable to maximally exert.
- Provides additional prognostic markers (see below).

Diagnostic Accuracy of Exercise ECG, Thallium Imaging, and Stress Echocardiography

<table>
<thead>
<tr>
<th>Definition of (+) test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+) Exercise ECG alone</td>
<td>.65</td>
<td>.85</td>
</tr>
<tr>
<td>(+) Thallium image alone</td>
<td>.84</td>
<td>.87</td>
</tr>
<tr>
<td>(+) Exercise ECG OR (+) thallium</td>
<td>.94</td>
<td>.74</td>
</tr>
<tr>
<td>(+) Exercise ECG AND (+) thallium</td>
<td>.55</td>
<td>.98</td>
</tr>
<tr>
<td>(+) Stress ECHO</td>
<td>.85</td>
<td>.77</td>
</tr>
</tbody>
</table>

Additional notes on nuclear imaging
- A common criterion for positivity is EITHER an abnormal ECG response or an abnormal image. Thus, the addition of thallium results in an increase in sensitivity at the expense of specificity (fewer false negatives but more false positives).
- Using specific patterns of uptake as predictors of left main or triple vessel disease, thallium EST has a sensitivity of 46% and specificity of 73% for detecting “surgical” disease (LR < 2).
- A completely negative thallium EST is an excellent predictor of a good prognosis (mortality rate less than 1% per year); however, that is also true for a treadmill ECG.
- The best use of nuclear imaging is in patients with uninterpretable ECGs and in submaximal ESTs after MIs. Nuclear imaging is also used to identify the functional effect of lesions prior to catheterization or angioplasty.
- ESTs of all types appear to be less specific (i.e. more false positives) in women.
- Use of right chest leads may increase sensitivity of the EST.

Alternative stress tests
- Dipyridamole myocardial perfusion imaging (persantine-thallium test) is useful in patients unable to exercise. Accuracy is similar to thallium EST. It is contraindicated in bronchospasm.
- Stress and dobutamine echocardiography are able to measure left ventricular function as a prognostic marker. Diagnostic accuracy is similar to myocardial perfusion imaging. Dobutamine infusion is contraindicated in atrial fibrillation and unstable angina.
- Dobutamine myocardial perfusion imaging is useful in patients with bronchospasm or asthma who are unable to exercise.
Electron beam CT (EBCT)
- Coronary calcification is associated with coronary obstructive disease by angiography.
- Studies assessing coronary calcification as an independent predictor of future coronary events have produced conflicting results.\(^\text{12,13}\)
- The American College of Cardiology and American Heart Association recently concluded that EBCT could not be routinely recommended for diagnosis of CAD but that it might be useful for identification of patients at high risk for developing CAD.\(^\text{14}\) Further investigation is required.

Risk stratification
- In addition to diagnosing coronary artery disease, exercise stress testing can identify patients at high risk for adverse outcomes. Revascularization should be considered in these patients even if symptoms are acceptably controlled.
- The Duke treadmill score\(^\text{15}\) is based on a routine exercise ECG test. It is a useful way to stratify patients with suspected CAD.

### Survival Based on Duke Treadmill ECG Test Scores\(^\text{15}\)

<table>
<thead>
<tr>
<th>Score</th>
<th>Percent</th>
<th>Four-year survival</th>
<th>Annual mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\geq +5)</td>
<td>62%</td>
<td>99%</td>
<td>0.25%</td>
</tr>
<tr>
<td>-10 to +4</td>
<td>34%</td>
<td>95%</td>
<td>1.25%</td>
</tr>
<tr>
<td>(\leq -10)</td>
<td>4%</td>
<td>79%</td>
<td>5.00%</td>
</tr>
</tbody>
</table>

- Note the excellent prognosis for most patients with low scores.
- Patients at intermediate or high risk should be assessed for high risk features by additional studies.

High risk features
- Clinical: left ventricular dysfunction (especially ejection fraction (EF) less than 35%), history of myocardial infarction, peripheral vascular disease, sudden death, or sustained ventricular tachycardia
- Treadmill exercise test: shorter duration of exercise, higher magnitude of ST segment depression, exertion limiting angina, drop in blood pressure
- Stress myocardial perfusion: wider distribution of ischemia, increased lung uptake
- Stress echocardiography: decrease in EF during exercise

A decision to perform a catheterization is favored by:
- increased severity of symptoms (e.g. with minimal exertion)
- instability of symptoms (e.g. new onset or rest angina)
- presence of high risk features (e.g. LV dysfunction)
- age of the patient (younger patients have lower risk of cath)
- failure of medications to adequately control symptoms
- desire of the patient to undergo the procedure.

### References


14. American College of Cardiology/American Heart Association. Expert Consensus Document on Electron-Beam Computed Tomography for the Diagnosis and Prognosis of Coronary Artery Disease. J Am Coll Cardiol 2000; 36;310–25. This report included a meta-analysis of diagnostic accuracy of EBCT: sensitivity was 90%, specificity was 50%. Overall accuracy (70%) was similar to that reported for other non-invasive tests.


The Duke treadmill test score = \([\text{exercise time in minutes}] - [5 \times \text{ST segment depression in mm}] - [4 \times \text{Angina Index}]\). The Angina Index = 0 if no angina occurs on EST, 1 if angina occurs, and 2 if angina is the reason for stopping the test.

Cardiac catheterization may be performed to:
- attain a diagnosis in a patient who is suspected to have CAD
- assess the extent of disease in a patient known to have CAD
- prepare for surgery or angioplasty when indicated.
Effective treatment of coronary artery disease requires patient education, risk factor modification, medical therapy, and, as indicated, coronary revascularization. The American College of Cardiology and American Heart Association have developed and promoted a treatment mnemonic for the 10 most important elements in the management of stable angina:16

Aspirin and antianginals
Beta blocker and blood pressure
Cholesterol and cigarettes
Diet and diabetes
Education and exercise

Risk factor modification
Smoking: the overall adverse effects disappear within three years of cessation. Thrombogenic effects disappear more rapidly.
Lipids: aggressive treatment of hyperlipidemia with statins reverses atherogenesis, prevents cardiovascular (CV) events, and saves lives in patients with CAD (see below).
Hypertension: treatment of hypertension reduces the risk of coronary events (especially when ACEIs are used – see below) and reverses left ventricular hypertrophy.
Diabetes mellitus: the benefit of glucose control in prevention of coronary events has not been conclusively demonstrated.17
Exercise and weight loss: Benefits are suspected but a reduction in coronary outcomes has not yet been proven in a trial.

Medications
Antiplatelet agents
Aspirin should be given to all patients with known or suspected CAD unless contraindicated. The standard dose is 80–325 mg qd. The use of low dose aspirin is associated with a 33% reduction in adverse coronary events.18
Dipyridamole (Persantine) exhibits antithrombotic properties and vasodilatory effects on coronary resistance vessels. The latter can actually decrease perfusion via stenotic vessels. Thus, dipyridamole should not be used as an antiplatelet agent.16
Ticlopidine (Ticlid) is a thienopyridine derivative that inhibits platelet aggregation but may cause severe neutropenia. It has not been shown to decrease coronary events.
Clopidogrel (Plavix) exerts a stronger antiplatelet effect than ticlopidine. In comparison with aspirin, clopidogrel was slightly more effective in preventing adverse outcomes in patients with cardiovascular disease.19 It is most useful in patients who cannot tolerate the gastric effects of aspirin.


17 UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;332:837–53. Intensive treatment of type 2 diabetes reduced the risk of myocardial infarction by a non-statistically significant 16% (ARR = 3 per 1000 patient years, P = 0.052).


19 Capri Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE). Lancet 1996;348:1329–39. Clopidogrel reduced the combined incidence of ischemic stroke, MI, or vascular death from 5.8% to 5.3% (RR = 9%, ARR = 0.5%). Because of its expense, clopidogrel is not considered a first line agent for stable angina.
The beta blockers

- Are first line agents for treatment of CAD. They are the only antianginals that prevent cardiovascular events (aspirin and ACEIs are not antianginals; calcium antagonists and nitrates do not prevent cardiovascular events). Long term treatment up to four years has reduced mortality from 12.2% to 9.7% in survivors of myocardial infarctions.20
- Are just as effective in anginal control and, contrary to popular opinion, better tolerated than calcium antagonists.21
- Have proven ability to prevent silent ischemia in CAD and to prevent sudden death and infarction in patients post myocardial infarction.
- May be used in diabetic patients but should be used with caution in patients on insulin (they blunt the response to hypoglycemia).
- Even cardioselective beta blockers can cause bronchospasm at antianginal doses. Asthma is a relative contraindication.
- Absolute contraindications to beta blockers include severe bradycardia, high degree atrioventricular block, sick sinus syndrome, and unstable heart failure.16

Nitrates

- Are effective in the treatment of symptoms but not proven to prevent adverse events. They are equally as effective as beta blockers in reducing anginal symptoms.21
- Provide additional antianginal effects in combination with beta blockers and calcium antagonists.22
- The sublingual form is appropriate to treat or prevent exertional chest pain and may be the treatment of choice in patients with rare symptoms. As prophylaxis, it may be taken immediately before exertional activity.
- Long term nitrates are effective in patients with more frequent symptoms but require staggered dosing to prevent tolerance. Isordil should be taken at 9 am, 1 pm, and 5 pm. Nitrate patches should be taken off in the evening to provide a “drug holiday”.

Calcium antagonists

- Are effective in reducing symptoms alone or in combination with beta blockers and nitrates.
- Are especially useful in patients with diabetes, asthma, or COPD, who may not tolerate beta blockers.
- Have no proven benefit in preventing adverse outcomes.
- Diltiazem and verapamil slow the heart rate and are a logical choice when no beta blocker is prescribed. They may be used alone or with nitrates.
- Amlodipine is a better choice to combine with beta blockers as it does not slow the heart rate.
- Short acting nifedipine is suspected of increasing CV mortality in some patient groups. Diltiazem may increase CV mortality in post MI patients with LV dysfunction.
In the IMAGE trial, combination therapy with metoprolol and nifedipine was superior to either drug alone.23

HMG-Coenzyme A reductase inhibitors (statins)
• Have proven ability to prevent adverse outcomes and should be used to lower LDL to <100 mg/dl. Their mechanism of action includes stabilization of existing coronary plaques.
• In a trial of over 4400 patients with known CAD and high LDL (mean 190 mg/dl), simvastatin lowered overall mortality from 11.5% to 8.2% over five years.24 The relative risk of coronary events was reduced by 42%.
• In a trial of patients with known CAD and moderately elevated LDL-C (mean 150 mg/dl) pravastatin prevented about two coronary deaths and four coronary events for every 100 patients treated for six years.25
• Gemfibrozil and nicotinic acid have both been shown to decrease coronary events and may be suitable alternatives to statins in patients with low HDL and high triglycerides.

Angiotensin converting enzyme inhibitors (ACEIs)
• Are growing in importance as agents of prevention. They should be used in diabetic patients and hypertensives with CAD.
• In the HOPE trial, ramipril 10 mg per day reduced CV events in patients over 55 years with known CAD or diabetes plus another CAD risk factor. About two strokes and two cardiovascular deaths were prevented in every 100 treated patients.26

A suggested strategy for medical therapy of stable angina
1. Aggressively pursue smoking cessation and lifestyle change.
2. Immediately start coated aspirin at 80–325 mg qd.
3. Start atenolol 25–50 mg qd (or metoprolol 25 mg bid) and titrate upward to resting heart rate of 55–60 and prevention of exertional symptoms. Use prophylactic sublingual NTG if indicated.
4. Add amlodipine 5–10 mg qd if still symptomatic after adequate dosing of atenolol. Consider isosorbide dinitrate 20–40 mg tid if angina persists or if a β blocker is contraindicated.
5. Begin a statin drug if LDL >100 mg/dl on diet.
6. Consider ACEI if diabetic or hypertensive.
7. Refer for catheterization if medical management fails OR the patient exhibits high risk features.

Indications for referral to cardiology
• Need for catheterization for diagnostic or prognostic purposes
• Failure of conventional medical therapy
• Complicating conditions – valvular disease, heart failure, etc.
• Evidence of high risk features (see below)
• Refractory angina in patients ineligible for procedures


Note – some medications (aspirin and ACEIs) prevent events but not symptoms; others (nitrates and calcium antagonists) reduce symptoms but not events; and others (β blockers) achieve both objectives.

Triple therapy with β blockers, nitrates, and calcium blockers probably adds little to double therapy.
Revascularization

Introduction
- Revascularization should be considered in patients who fail medical management or who exhibit high risk features.
- The choices for revascularization include percutaneous transluminal coronary angioplasty (PTCA), with or without stenting, and coronary artery bypass grafting (CABG).

CABG versus medical management
- Three large trials were conducted in the 1970s: the Coronary Artery Surgery Study (CASS), the European Coronary Surgery Study (ECSS), and the Veterans’ Administration Cooperative Study (VA Study).
- A meta-analysis of these studies demonstrated the following outcomes.  

<table>
<thead>
<tr>
<th>Disease</th>
<th>Medical (%)</th>
<th>Surgery (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left main</td>
<td>36.5</td>
<td>15.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>3 vessel</td>
<td>17.6</td>
<td>11.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>2 vessel</td>
<td>11.7</td>
<td>10.0</td>
<td>NS</td>
</tr>
<tr>
<td>1 vessel</td>
<td>9.9</td>
<td>5.6</td>
<td>NS</td>
</tr>
<tr>
<td>Abnormal LV function</td>
<td>25.2</td>
<td>16.6</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

- For patients without a proximal LAD lesion, surgery improved survival only in those with left main or three vessel disease.
- For patients with a proximal LAD lesion, surgery improved survival in those with two or three vessel disease.

PTCA versus medical management
- In the ACME trial, patients with one vessel disease and exercise induced ischemia who were randomized to PTCA were more likely (64%) to be free of angina than medically managed patients (46%).
- In the RITA-2 trial, patients with 1–3 diseased vessels who were randomized to PTCA were slightly more likely to be free of antianginals than medical patients at one year (20% versus 7%); however, PTCA patients were significantly more likely to experience the primary outcome of death or definite MI (6.3% versus 3.0%).

Revascularization versus medical management
- In the ACIP Study, patients with CAD who were well-controlled on medications but who had documented silent ischemia were randomized to revascularization (CABG or PTCA at physician discretion) or medical management.
- Revascularized patients had lower mortality (1.1% v 5.5%), especially within the subgroup with proximal LAD lesions (3.3% v 13.3%).
- The MASS study compared medical management, PTCA, and CABG in a three arm trial of patients with solitary

Overall Mortality at 5, 7 and 10 Years

<table>
<thead>
<tr>
<th></th>
<th>Medical</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 years</td>
<td>15.8%</td>
<td>10.2%</td>
</tr>
<tr>
<td>7 years</td>
<td>21.7%</td>
<td>15.8%</td>
</tr>
<tr>
<td>10 years</td>
<td>30.5%</td>
<td>26.4%</td>
</tr>
</tbody>
</table>

Although revascularization procedures have been studied extensively, most studies were performed prior to the extensive use of stents and modern medical therapy. The use of these modalities would likely improve the outcomes of all revascularized patients.


29 RITA-2 Trial Participants. Coronary angioplasty versus medical therapy for angina: the second Randomised Intervention Treatment of Angina (RITA-2) trial. Lancet 1997;350:461–8. There was a higher risk of myocardial infarction in PTCA patients due to transient enzyme elevations that occurred at the time of the procedure.

30 Davies RF, Goldberg AD, Forman S et al. Asymptomatic Cardiac Ischemia Pilot (ACIP) study two-year follow-up: outcomes of patients randomized to initial strategies of medical therapy versus revascularization. Circulation 1997;95:2037–43. Many of these patients exhibited high risk features. The average degree of ST segment depression on EST was 2.4 mm.
severe proximal LAD lesions. At three years, mortality rates were similar in all groups, but revascularized patients were more likely to be angina free (CABG 98%, PTCA 82%, medical 32%).

**PTCA versus CABG**

- Typically studies included only the subset of patients with lesions amenable to angioplasty and did not include stenting.
- The largest of these, the BARI trial, randomized a diverse group of patients with multivessel disease to CABG or PTCA. All subjects had lesions amenable to PTCA. The study showed a survival benefit that was entirely confined to the subset of patients with diabetes.

### BARI Trial Mortality Rates at Seven Years

<table>
<thead>
<tr>
<th>Subset</th>
<th>CABG(%)</th>
<th>PTCA (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>15.6</td>
<td>19.1</td>
<td>0.04</td>
</tr>
<tr>
<td>Diabetic patients</td>
<td>23.6</td>
<td>44.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>Non-diabetic patients</td>
<td>13.6</td>
<td>13.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

- In patients without diabetes, outcomes were identical between CABG and PTCA whether or not patients had three vessel disease, proximal LAD disease, or LV dysfunction.

**Summary and conclusions**

Multiple trials have demonstrated a benefit of revascularization in control of symptoms and survival for specific subsets of patients. In patients with lesions amenable to angioplasty, the survival advantage of CABG over PTCA may be confined to the subset with diabetes.

Acceptable revascularization strategies include the following

- CABG in patients with significant left main coronary disease
- CABG or PTCA in non-diabetic patients with significant three vessel or two vessel disease and proximal LAD stenosis
- CABG in diabetic patients with two or three vessel disease requiring revascularization
- CABG or PTCA in patients with one or two vessel disease with a large area of myocardium at risk
- CABG or PTCA in patients for whom medication fails to control symptoms

31 Hueb WA, Bellotti G, de Oliveira SA et al. The Medicine, Angioplasty or Surgery Study (MASS): a prospective, randomized trial of medical therapy, balloon angioplasty, or bypass surgery for single proximal left anterior descending artery stenoses. J Am Coll Cardiol 1995;26:1600–5. The MASS trial subjects appeared to be at lower risk than ACIP trial patients. There were very low event rates in all three arms.

32 The BARI Investigators. Seven-year outcome in the Bypass Angioplasty Revascularization Investigation (BARI) by treatment and diabetic status. J Am Coll Cardiol 2000;35:1122–9. All subsets of diabetic patients derived equal benefit from CABG, even those with mild symptoms, normal LV function, double vessel disease, or no LAD lesions. In non-diabetic patients, mortality outcomes were equal across all subgroups but CABG patients had a lower rate of subsequent revascularization (13% versus 60%).

The much smaller EAST study also compared PTCA to CABG. The outcomes were essentially the same in both arms. There were trends favoring surgery in patients with LAD stenoses and in patients with diabetes but they were not statistically significant in these relatively small subgroups (there were only 59 diabetic patients enrolled). King SB, Kosinski AS, Gayton RA et al. Eight year mortality in the Emory Angioplasty Versus Surgery Trial (EAST). J Am Coll Cardiol 2000;35:1116–21.
Table 10.1 Agents for Coronary Artery Disease.

<table>
<thead>
<tr>
<th>Type of drug</th>
<th>Dosage forms (mg)</th>
<th>Usual dosage (mg)</th>
<th>Adverse effects, comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiplatelet agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>81/325</td>
<td>81–325 qd</td>
<td>Gastritis, PUD, GI bleed</td>
</tr>
<tr>
<td>Coated aspirin (Ecotrin)</td>
<td>325</td>
<td>325 qd</td>
<td>Less incidence of gastritis</td>
</tr>
<tr>
<td>Dipyridamole (Persantine)</td>
<td>25/50/75</td>
<td>75–100 qd</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Clopidogrel (Plavix)</td>
<td>75</td>
<td>75 qd</td>
<td></td>
</tr>
<tr>
<td>Ticlopidine (Ticlid)</td>
<td>250</td>
<td>250 bid</td>
<td>Diarrhea, N and V, GI pain, severe neutropenia in 1% of patients (check CBC q 2 wks x 12 wks)</td>
</tr>
<tr>
<td><strong>β Blockers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propranolol (Inderal)</td>
<td>10/20/40/60/80</td>
<td>10–80 qid</td>
<td>Short acting</td>
</tr>
<tr>
<td>Atenolol (Tenormin)</td>
<td>25/50/100</td>
<td>25–200 qd</td>
<td>Cardioselective, least CNS effect</td>
</tr>
<tr>
<td>Metoprolol (Lopressor)</td>
<td>50/100</td>
<td>50–200 bid</td>
<td>Cardioselective</td>
</tr>
<tr>
<td>Nadolol (Corgard)</td>
<td>20/40/80/160</td>
<td>40–320 qd</td>
<td>Not cardioselective</td>
</tr>
<tr>
<td>Pindolol (Visken)</td>
<td>5/10</td>
<td>5–10 bid</td>
<td>Partial agonist</td>
</tr>
<tr>
<td><strong>Calcium channel blockers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nifedipine (Procardia)</td>
<td>10/20</td>
<td>10–40 tid</td>
<td>Pedal edema, reflex tachycardia</td>
</tr>
<tr>
<td>Nifedipine XL (Procardia XL)</td>
<td>30/60/90</td>
<td>30–90 qd</td>
<td>? Safer than nifedipine (see text)</td>
</tr>
<tr>
<td>Diltiazem (Cardizem)</td>
<td>30/60/90/120</td>
<td>30–90 qid</td>
<td>Bradycardia, heart block</td>
</tr>
<tr>
<td>Diltiazem CD (Tiazac)</td>
<td>120/180/240/300</td>
<td>120–300 qd</td>
<td></td>
</tr>
<tr>
<td>Verapamil (Calan, Isoptin)</td>
<td>40/80/120</td>
<td>80–120 tid</td>
<td>Bradycardia, heart block, CHF</td>
</tr>
<tr>
<td>Verapamil SR (Calan SR)</td>
<td>120/180/240</td>
<td>180 qd–180 bid</td>
<td></td>
</tr>
<tr>
<td>Isradipine (DynaCirc)</td>
<td>2.5/5</td>
<td>2.5–5 bid</td>
<td>Pedal edema, reflex tachycardia</td>
</tr>
<tr>
<td>Amlodipine (Norvase)</td>
<td>2.5/5/10</td>
<td>2.5–10 qd</td>
<td>Pedal edema</td>
</tr>
<tr>
<td><strong>Nitrates</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin (Nitrostat)</td>
<td>0.3/0.4/0.6</td>
<td>1–2 tabs SL prn</td>
<td>Headache, hypotension for all nitro preparations; Isordil should be dosed at 9 am, 1 pm, and 5 pm</td>
</tr>
<tr>
<td>Isosorbide dinitrate (Isordil)</td>
<td>5/10/20/30/40</td>
<td>1–40 qid</td>
<td></td>
</tr>
<tr>
<td>Isosorbide dinitrate SR (Tembids)</td>
<td>40</td>
<td>40–80 bid</td>
<td></td>
</tr>
<tr>
<td>Isosorbide mononitrate (ISMO)</td>
<td>20</td>
<td>20 bid</td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin patch (Nitro-Dur, Nitro-Bid, Transderm)</td>
<td>5 cm², 10 cm², 20 cm², 30 cm²</td>
<td>1 patch qd</td>
<td>Patches should be removed in the evening to prevent tolerance</td>
</tr>
<tr>
<td>Nitroglycerin ointment 2%</td>
<td></td>
<td>1–2 inches tid</td>
<td></td>
</tr>
</tbody>
</table>
11 Cough, bronchitis, and pneumonia
Sondra Zabar and Danielle Ofri

Cough and bronchitis

Epidemiology

Incidence

• Cough accounted for nearly 30 million office visits in 1997.1
• It is the most common symptomatic reason for ambulatory care visits.

Etiology

Acute cough: <3 weeks duration2
• Common cold (the most common etiology) with postnasal drip
• Other infections: acute bronchitis, sinusitis, pneumonia, PCP, tuberculosis, pertussis
• Irritation: allergic rhinitis, smoking, other environmental irritants.
• Bronchospasm: asthma, ACE inhibitors
• Other underlying disease: heart failure, pulmonary embolism

Chronic cough: >3 weeks duration
Often due to more than one condition.3 In most studies, the first three conditions listed account for 75–90% of all chronic cough.
• Postnasal drip (most common)
• Asthma (cough variant asthma)
• Gastroesophageal reflux disease (GERD)
• Chronic bronchitis
• ACE inhibitors
• Lung cancer
• Bronchiectasis
• Interstitial lung disease
• Psychogenic

Diagnosis

History

• Duration: acute versus chronic
• Frequency: seasonal versus specific exposure
• Severity: disruption of sleep or daily activities
• Fever
• Sputum color and quality
• Presence of hemoptysis
• Smoking history
• Weight loss
• HIV status
• Dyspnea or episodic wheezing (asthma)
• Tickle or drip in throat, nasal discharge or frequent clearing of throat (postnasal drip)


3 Mello CJ, Irwin RS, Curley FJ. Predictive value of the character, timing, and complications of chronic cough in diagnosing its cause. Arch Intern Med 1996;156:997–1003. In this prospective study of 88 patients in a referral clinic with chronic cough, GERD, postnasal drip, and asthma accounted for 90% of diagnoses (a majority had >1 cause). Detailed history of character, timing, and complications of cough was not helpful in predicting etiology.
Sour taste, heartburn, nocturnal cough (GERD)
Precipitating factors: smoke or specific environmental agent

Physical exam
Vital signs: temperature, respiratory rate
Throat: cobblestone appearance of the mucosa (from chronic stimulation of the submucosal lymphoid follicles secondary to postnasal drip)
Chest: wheezing, dullness, rhonchi

Diagnostic tests
Sputum gram stain and culture: there are no studies looking at the utility of sputum evaluation in outpatients. Tests are usually limited by inability of the patient to provide an adequate specimen.
Chest radiograph: indications include fever, dyspnea, weight loss, smoking history, immunocompromise, and hemoptysis.
Other tests: pulmonary function tests, gastric pH monitoring, sinus imaging, CT, as determined by degree of suspicion of particular syndromes.

Clinical syndromes
Postnasal drip
This syndrome can be caused by the common cold, allergic and non-allergic rhinitis, sinusitis, and environmental irritants.
The diagnosis is made by history (a feeling of something in the throat, the need to clear one’s throat, nasal congestion) and the response to treatment.
Because of the frequency of this syndrome, some experts recommend an empiric trial of antihistamines and/or decongestants for all patients with cough. This has been shown to decrease cough in patients with postnasal drip due to the common cold.
In patients with allergic rhinitis, intranasal steroids appear to provide more benefits than oral antihistamines, with fewer side effects.

Asthma
Asthma may present as isolated cough (cough variant asthma) or cough in the presence of classic symptoms of wheezing and chest tightness.
The diagnosis of cough variant asthma can be difficult. The cough may be exacerbated by viral illness, exercise, cold air, or environmental irritants.
Pulmonary function tests, even in the presence of provocative stimuli such as methacholine or cold air, may not provide the diagnosis.
The diagnosis is often made only by response to treatment with inhaled β agonists or corticosteroids.

**Gastroesophageal reflux disease (GERD)**
- Cough may be precipitated by aspiration of gastric contents or by direct stimulation of the nerves involved in the cough reflex.\(^8\)
- Patients may not exhibit the classic symptoms of sour taste, heartburn, and sense of reflux.
- Diagnosis can be made by upper GI series or 24-hour esophageal pH monitoring, but often an empiric trial of H\(_2\) blockers or proton pump inhibitors is simpler.\(^9\)

**Acute bronchitis**
- Acute bronchitis is most commonly due to viruses and atypical pathogens. Along with cough, there is some transient airway hyperreactivity.\(^10\)
- It is difficult to distinguish viral from bacterial causes of bronchitis.
- The central controversy surrounding acute bronchitis is whether or not to treat with antibiotics.
- Acute bronchitis is a self-limited illness, but many patients expect antibiotics and are disappointed if they are not prescribed.
- Most randomized trials have not shown benefits of antibiotics over placebo in patients without asthma or other underlying lung disease.\(^11\) Although recent meta-analyses have come to conflicting conclusions, even those that have demonstrated a benefit have noted that the benefit is generally small and is accompanied by a commensurate increase in side effects.\(^12\)
- For patients with cough or wheezing, inhaled β agonists sometimes diminish symptoms.\(^13\)
- Patients may also find relief with simple pain relievers and antitussive medications (see below).
- Stable patients without underlying lung pathology can usually be safely managed without antibiotics.\(^14\)

**Chronic bronchitis**
- Chronic bronchitis is defined as the presence of cough and sputum production on most days for at least three months for at least two consecutive years in a patient in whom other causes of chronic cough have been excluded.
- Cessation of cigarette smoking can improve the cough\(^15\) and is the most clinically long term treatment.
- Inhaled ipratropium bromide is the mainstay of treatment and can decrease the amount of sputum production.\(^16\)
- Inhaled β agonists are also considered first line therapy, but they have not been evaluated specifically in terms of cough or sputum production in chronic bronchitis.
- Theophylline is often used with patients who do not achieve improvements in air flow with inhaled bronchodilators, but its narrow therapeutic window and numerous drug interactions limit its use.
• Inhaled corticosteroids diminish airway reactivity but there is no effect on cough and sputum production. It is unclear whether they have any long term effect on lung function.
• Antibiotics are generally recommended for acute exacerbations but have little role in chronic stable bronchitis.
• Other treatments that may be helpful include pulmonary rehab, nutritional support, and supplemental oxygen in patients with severe hypoxemia.

ACE inhibitors
• Dry cough is a side effect of all ACE inhibitors and does not appear to be dose dependent. About 10% of patients experience cough which persists if a different ACE inhibitor is substituted.
• It is described as a non-productive cough associated with tickling or irritation in the throat. Cough can develop at any time after initiating therapy with ACE inhibitors. After cessation of drugs, the cough usually resolves within four weeks.
• The cough is likely due to increased levels of bradykinin, substance P, and prostaglandins. Angiotensin receptor blocking agents do not cause accumulation of these mediators and have not been associated with cough.
• Anyone with a cough who is taking an ACE inhibitor for any length of time should have a trial off medications for at least four weeks.

Bronchiectasis
• Bronchiectasis is characterized by subsegmental bronchial damage from chronic inflammation usually secondary to chronic or recurrent infections. Typically there is a damaging synergistic cycle of repeated insults and abnormal host defenses. Cystic fibrosis, tuberculosis, mycobacterium avium complex (MAC) infections, and allergic bronchopulmonary aspergillosis are all important predisposing conditions.
• Patients present with a chronic cough that is usually purulent. Diagnosis is most easily made with high resolution CT.
• Patients diagnosed with bronchiectasis should be screened for tuberculosis and referred to a pulmonologist.
• Treatment involves chest physiotherapy, antibiotics, bronchodilators, and inhaled corticosteroids, although most studies examining these modalities have been small. In some patients, there may be a role for surgical intervention.

Postinfectious cough
• Some patients experience a cough after an infection has resolved. This can happen with any infection, but Pertussis, Mycoplasma, and Chlamydia appear to be the most common offenders.
• In the presence of a normal chest radiograph, this cough usually improves on its own, with a variable time course.
Some clinicians use inhaled corticosteroids or ipratropium, but these have not been studied except in small trials.21

**Lung Cancer**
- Bronchogenic tumors cause cough by irritation of the cough receptors. This is more common with centrally located tumors (squamous cell and small cell) than those located more distally where there are fewer such receptors.
- Cough is a common symptom of cancer, but cancer is a rare cause of chronic cough.
- Lung cancer is rare in non-smokers, although bronchoalveolar adenocarcinoma appears to be the one subtype that is not related to tobacco exposure. Asbestos exposure is another factor in non-smokers (and smokers) that increases the risk of cancer.
- Cough in current or former smokers should be pursued aggressively if not resolved within four weeks, even if a chest radiograph is normal.
- Diagnostic modalities include sputum cytology, CT, and bronchoscopy.22

**Chronic interstitial lung disease**
- Is usually characterized by dyspnea, but cough may be the predominant symptom.

**Psychogenic cough**
- Is a diagnosis of exclusion.
- Is more common in children than adults.
- While it may represent malingering, it can be a conversion symptom related to other psychosocial stressors.23

**Chronic cough algorithms**

There are several algorithms available for evaluation of chronic cough in immunocompetent patients. Since no diagnostic tests are definitive, actual diagnosis is usually retrospective and defined by resolution of cough with therapy. The protocols vary in how soon to obtain a chest radiograph.
- The American College of Chest Physicians24 recommends a chest radiograph if discontinuation of ACE inhibitor does not lead to resolution of cough, with the exception of young, healthy individuals with suspected postnasal drip. If the chest radiograph is normal, evaluation for postnasal drip, asthma, and GERD follows.
- Pratter et al.25 recommend initial empiric treatment for postnasal drip with an antihistamine and decongestant. This is followed by evaluation for asthma and postinfectious cough with pulmonary function tests (PFTs) with methacholine challenge. Chest and sinus films are recommended only if PFTs are negative or treatment with inhaled β agonists is not successful.
- Both protocols claim to diagnose and successfully treat 80–90% of patients in prospective evaluations.

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Treatment for cough
There is only limited evidence for most treatments. The main principle is to treat the underlying cause.

Antitussives
- Dextromethorphan hydrobromide: an over the counter, non-narcotic cough suppressant found in most cough syrups and pills.
- Benzonatate: a peripherally acting non-opioid
- Codeine

Expectorants
- Guaifenesin: an over the counter expectorant, commonly combined with dextromethorphan.

Community acquired pneumonia
Epidemiology
Incidence
- The incidence of pneumonia, as well as the complication rate, increases with age.
- Pneumonia/influenza was responsible for 91,871 deaths in 1998 – the number 6 cause of death in the US.
- Smoking is a risk factor for pneumonia.

Etiology
- Most etiology studies have been performed on hospitalized patients; it is difficult to apply these data to outpatients.
- The common pathogens include:
  - *Streptococcus pneumoniae*
  - respiratory viruses: influenza, respiratory syncytial virus
  - *Haemophilus influenzae*
  - atypical pathogens: Mycoplasma, Chlamydia
- Less common pathogens are Legionella, Staphylococcus, and Gram-negative organisms.
- The prevalence of various pathogens is affected by age, comorbidity, and setting (nursing home, prison, general community).
- While identification of a causative pathogen can direct therapy, this process is often difficult and impractical and has not been shown to alter outcome.

Diagnosis
- Classic signs and symptoms of pneumonia include cough, sputum production, fever, dyspnea, crackles, tachypnea, egophony, and dullness to percussion.
- None of these clinical findings, however, has been shown to have sufficient statistical power to rule in or rule out the diagnosis of pneumonia. Furthermore, there is surprisingly little interobserver reliability in detecting the presence or absence of the signs of pneumonia.
• Several clinical prediction rules exist which agree, in general, that a normal chest exam and normal vital signs substantially lower the probability of pneumonia.

• As with many other diseases, presentation of pneumonia in elderly patients may be atypical. Older patients tend to report fewer non-respiratory symptoms (fever, chills, sweats, myalgias). This may be because they are less likely to mount a febrile response to infection.

• There are also few data about the utility of the chest radiograph.

• There is reasonably good interobserver reliability between radiologists about the presence or absence of infiltrate, pleural effusions, and multilobar involvement. This reliability is about the presence or absence of infiltrate, pleural effusions, and multilobar involvement. Among 282 radiographs, two radiologists agreed 85% of the time about the presence or absence of an infiltrate.

• The presence of pleural effusion and multilobar involvement are independent predictors of increased mortality.

Treatment

Whom to admit to hospital

• Beyond making the diagnosis, this is the central question in the evaluation of pneumonia in outpatients.

• Clinical prediction rules have been developed to answer this question, but none has been adequately validated with prospective, randomized, controlled trials.

• These rules have been derived from studies that sought to correlate clinical characteristics with patient outcomes. The studies vary markedly in patient population and settings, making generalizability difficult.

• A recent meta-analysis identified hypothermia, hypotension, tachypnea, neoplastic or neurologic disease, bacteremia, leukopenia, and multilobar disease as factors that increased mortality, with odds ratios of 3–5. (The OR for diabetes mellitus was 1.3.) Mortality for outpatients was 5%. In practice, this does little to refine the basic procedure of admitting patients with abnormal vital signs, severe underlying disease, or lack of home care support.

Antibiotic therapy

Treatment for pneumonia is usually empirical. Several groups have published treatment guidelines for outpatient therapy.

Infectious Disease Society of America guidelines

• Class I and II can be treated as outpatients; expected mortality is <1%
  —Recommended outpatient antibiotics include: macrolides, fluoroquinolones, or doxycycline.
  —Alternative antibiotics include: amoxicillin/clavulanate or second-generation cephalosporin.
  —Modifying factors include: suspected penicillin resistance (fluoroquinolones), suspected aspiration (amoxicillin/clavulanate), young adult aged 17–40 (doxycycline).

• Class III may require brief inpatient treatment; expected mortality is 2.8%.

Scoring system

<table>
<thead>
<tr>
<th>Points</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>+10</td>
</tr>
<tr>
<td>Gender</td>
<td>+10</td>
</tr>
<tr>
<td>Comorbid illness</td>
<td>+10</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>+10</td>
</tr>
<tr>
<td>Liver disease</td>
<td>+10</td>
</tr>
</tbody>
</table>
Class IV and V require inpatient treatment; expected mortality is 8% and 29% respectively.

—Recommended inpatient antibiotics include: β-lactam ± macrolide, fluoroquinolone.
—Alternative antibiotics include: cefuroxime ± macrolide, azithromycin.
—Modifying factors include: ICU requirement, structural disease, aspiration.

Prevention

Pneumonia

Pneumococcal vaccination with the 23-valent polysaccharide vaccine has been shown to reduce the incidence of pneumococcal bacteremia, but has not affected overall mortality rates.

—Vaccination may reduce the risk of contracting pneumonia in the elderly.
—The pneumococcal vaccine may be given at the same time as the influenza vaccine, in the other arm.

Guidelines for pneumococcal vaccine

The Advisory Committee on Immunization Practices recommends pneumococcal vaccine for the following groups.

• All persons ≥65 years
• Anyone aged 2–65 years at higher risk for poor outcomes with pneumococcal disease
• Underlying chronic illness
• Functional or anatomic asplenia
• People living in environments in which the risk for disease is high
• Immunocompromised state
• Revaccination is not recommended for immunocompetent people, but may be considered after five years in high risk patients with illnesses that may contribute to rapid antibody decline (asplenia, nephrotic syndrome, HIV, malignancy, bone marrow suppression, chronic steroid use).

Influenza

• Influenza infection leads to both viral pneumonia and secondary bacterial pneumonia.
• Influenza vaccination of the elderly has been shown to reduce the incidence of pneumonia, hospital admission, and mortality.
• Immunization of healthcare workers benefits their patients.

Guidelines for influenza vaccine

The Advisory Committee on Immunization Practices recommends influenza vaccine for the following groups.

• All persons >50 years (reduced from age 65)
• Residents of nursing homes and chronic care facilities

Physical exam

<table>
<thead>
<tr>
<th>Points</th>
<th>Class</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 70</td>
<td>II</td>
<td>Low</td>
</tr>
<tr>
<td>71–90</td>
<td>III</td>
<td>Low</td>
</tr>
<tr>
<td>91–130</td>
<td>IV</td>
<td>Moderate</td>
</tr>
<tr>
<td>&gt; 130</td>
<td>V</td>
<td>High</td>
</tr>
</tbody>
</table>

* Class I if age under 50, no comorbid disease, and no abnormal labs or physical findings

BUN = Blood urea nitrogen


• All persons with severe underlying chronic illness, including asthma and diabetes
• All children and teenagers (aged six months to 18 years) who are receiving long term aspirin therapy and therefore might be at risk for developing Reye’s syndrome after influenza infection
• All women who will be in the second or third trimester of pregnancy during the influenza season
• Healthcare workers in all settings, employees of chronic care facilities
• Household members (including children) of high risk patients.

Table 11.1 Agents for cough.

<table>
<thead>
<tr>
<th>Type of medication</th>
<th>Dosage forms</th>
<th>Usual dosage</th>
<th>Adverse effects, comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>15, 30 mg tabs</td>
<td>15–30 mg PO q6h</td>
<td>Schedule II narcotic. At higher than recommended doses, can cause nausea, vomiting, constipation, dry mouth, and sedation</td>
</tr>
<tr>
<td>Dextromethorphan*</td>
<td>10 mg/5 ml</td>
<td>20 mg PO q4h</td>
<td>Non-narcotic opiate. No sedative or analgesic effects</td>
</tr>
<tr>
<td>Benzonatate (Tessalon)</td>
<td>100 mg tabs</td>
<td>1–2 tabs PO tid</td>
<td>Sedation, headache, dizziness</td>
</tr>
<tr>
<td>Guaifenesin (Robitussin)</td>
<td>100 mg/5 ml</td>
<td>200 mg PO q4h</td>
<td></td>
</tr>
<tr>
<td>Guaifenesin (Humabid)</td>
<td>600 mg tabs</td>
<td>1–2 tabs PO q12h</td>
<td></td>
</tr>
</tbody>
</table>

* Robitussin-DM contains guaifenesin 100 mg and dextromethorphan 10 mg per 5 ml
12 Depression, anxiety, and somatization  
Joseph Rabatin and Lynn Buckvar-Keltz

Depression
Epidemiology
• The US lifetime prevalence rates of major depression and dysthymia are 17.1% and 6.4%, respectively. The one year prevalence of these disorders is 10.3% and 2.5% respectively.
• Women are affected ~1.8 times as often as men.
• Depression is more common in patients with a prior history of depression, a family history of depression, and in patients who are young, single, divorced, or seriously ill.
• More than 50% of patients with a history of major depression will have a recurrence.

Diagnosis
• Primary care physicians fail to recognize depression in >50% of their patients with the disorder.
• Many patients with depression present to their physician with somatic complaints, not with feeling “sad”.
• The complaints of patients presenting to primary care providers include anxiety, sleep disturbance, fatigue, and pain syndromes.
• Other medical disorders that may cause fatigue, insomnia, problems with memory, or other symptoms of depression should be considered. Check a complete blood count, urinalysis, and chemistry profile, as well as thyroid stimulating hormone and vitamin B₁₂ levels as appropriate.
• Ask about medicines and drug use that may affect mood.
  — Pharmacologic agents associated with depression include glucocorticoids, anabolic steroids, and phenobarbital.
  — It is unclear whether or not β blockers, carbamazepine, α methylidopa, or L-dopa contribute to depression.
  — Depression occurs during withdrawal from cocaine and amphetamines.
• Refer to the DSM-IV criteria at right for other symptoms.

Odds for Specific Depression Symptoms in Patients Who Seek Care in General Medical v Mental Health Settings

<table>
<thead>
<tr>
<th>Depression symptom</th>
<th>OR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysphoria</td>
<td>0.57</td>
<td>(0.38 to 0.84)</td>
</tr>
<tr>
<td>Worthless/sinful/guilty</td>
<td>0.63</td>
<td>(0.40 to 0.98)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1.71</td>
<td>(1.09 to 2.69)</td>
</tr>
<tr>
<td>Suicidal ideation/behavior</td>
<td>0.96</td>
<td>(0.66 to 1.41)</td>
</tr>
</tbody>
</table>

The lugubrious lexicographer
Dr Samuel Johnson, author of one of the first comprehensive dictionaries of the English language, describes his depression: “...I was overwhelmed with a horrible hypochondria, with perpetual irritation, with a dejection, gloom, and despair which made existence misery”. Years later, he wrote in the preface to his dictionary: “It was written... in sadness. Most of those whom I have wished to please have sunken into the grave... I, therefore dismiss it...” Morrant C. The melancholy of Dr. Samuel Johnson. Can Med Assoc J 1987; 136:201–3.

DSM-IV criteria for major depression
1. Depressed mood and/or anhedonia in nearly all activities for ≥ 2 weeks AND...
2. At least four of the following symptoms have been present during the same two week period and represent a change from previous functioning:
  • change in sleep pattern
  • fatigue
  • change in appetite or weight
  • change in psychomotor activity
  • feelings of worthlessness or guilt
  • difficulty thinking, concentrating, or making decisions
  • recurrent thoughts of death and/or suicidal ideation.

A useful brief questionnaire

- Multiple patient questionnaires have been assessed as screening tests for depression. Their overall sensitivity is 84% and specificity is 72%.4
- Sensitivity and specificity for a positive answer to one of the following questions are 95% and 57%.5
  1. “During the past month, have you often been bothered by feeling down, depressed, or hopeless?”
  2. “During the past month, have you often been bothered by little interest or pleasure in doing things?”
- Routine screening for depression in asymptomatic primary care patients received a “C” rating from the USPSTF because there is insufficient evidence to show that early detection and treatment of depression lead to improved outcome.6 A high index of suspicion is recommended in patients with a family history of depression, chronic illness, a recent loss, sleep disorder, chronic pain, or multiple unexplained symptoms.
- All patients with depression should be evaluated for a history of manic disorders to rule out bipolar disorder. Patients should also be evaluated for general medical disorders, substance abuse, and medications that may affect mood.

Treatment

Pharmacotherapy

- All depressed patients should be considered for treatment with medication. The results of a systematic review of 315 randomized trials of antidepressants are summarized in the table below.

<table>
<thead>
<tr>
<th>Patients with Major Depression Treated with New v Old Antidepressants v Placebo: Rate of Clinical Response7</th>
<th>Percent of patients with 50% reduction in symptoms (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comparison 1</strong></td>
<td></td>
</tr>
<tr>
<td>Newer antidepressants v</td>
<td>51</td>
</tr>
<tr>
<td>Placebo</td>
<td>32</td>
</tr>
<tr>
<td><strong>Comparison 2</strong></td>
<td></td>
</tr>
<tr>
<td>Newer antidepressants v</td>
<td>54</td>
</tr>
<tr>
<td>Older antidepressants</td>
<td>54</td>
</tr>
</tbody>
</table>
- A 4–6 week course of medication usually results in at least a partial response. A complete or near complete response usually takes 10–12 weeks.
- If there is no response at six weeks or only a partial response at 12 weeks, it is reasonable to consider other agents or referral to a psychiatrist for augmentation (addition of mood stabilizing agents such as lithium) or addition of psychotherapy.8
- When anxiety is a prominent symptom in depression, temporary adjunctive use of benzodiazepines for 1–4 weeks may be helpful.

3 Suh T, Gallo JJ. Symptom profiles of depression among general medical service users compared with specialty mental health service users. Psychol Med 1997;27:1051–63. Retrospective analysis of 5294 patients. Conclusion: In medical settings, depression is more likely to be expressed as a medical (fatigue) than a psychiatric (dysphoria) problem.
8 The efficacy of drug treatments for dysthymia: a systematic review and meta-analysis. Psychol Med 1999;29: 1273–89. Meta-analysis of 5437 patients in 15 trials. There was no difference between different classes of antidepressants.
Treatment should continue for at least 4–5 months after symptoms have resolved. Medications should then be tapered and patients followed up for recurrence of depressive symptoms.

Selective serotonin reuptake inhibitors (SSRIs)
- Members of this class include fluoxetine, sertraline, paroxetine, and citalopram.
- These drugs have become first line because they are effective, have few side effects, and are safe in overdose.
- Common side effects include GI symptoms (nausea, diarrhea), CNS symptoms (headache, agitation, insomnia, anorexia, tremor), and sexual dysfunction.
- The starting dose is usually the treatment dose.

Tricyclic antidepressants (TCAs)
- These drugs have significant side effects including anticholinergic effects (dry mouth, blurred vision, constipation, urinary hesitancy), postural hypotension, cardiac conduction delay, and decrease in seizure threshold.
- There is a narrow therapeutic range, making it easy to overdose and successfully commit suicide.
- The starting dose should be low and gradually increased.
- The secondary amines desipramine and nortriptyline cause less sedation, orthostatic hypotension, and anticholinergic effects than the tertiary amines amitriptyline, imipramine, and doxepin.
- For depressed patients with insomnia, adding a bedtime dose of trazodone, a benzodiazepine, or a sedating TCA is helpful.

Other antidepressants
- Bupropion: is stimulating. There is a risk of seizures at high doses.
- Venlafaxine: side effects are similar to those of SSRIs. It may cause high blood pressure.
- Trazodone: is sedating. It is often given at bedtime in combination with a morning dose of either bupropion or an SSRI to patients who also have insomnia.

Botanicals: St John’s wort
A systematic review of 27 trials of St John’s wort (Hypericum) found it more effective than placebo for short term treatment of mild to moderate depression. No difference was detected between this agent and conventional antidepressants.9

Rate of Patients With 50% Reduction in Symptoms Taking St John’s Wort

<table>
<thead>
<tr>
<th>Patients with response (%)</th>
<th>Patients with response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>St John’s wort</td>
<td>56</td>
</tr>
<tr>
<td>Placebo</td>
<td>25</td>
</tr>
</tbody>
</table>

Methods in cognitive therapy
- Patients should keep a diary monitoring situations, thoughts, and feelings.
- They should identify connections between thoughts, moods, and behavior.
- They should examine evidence for and against negative thoughts.
- Coach patients in how to challenge negative thoughts with questions and rationalizing techniques.
- Teach patients to identify dysfunctional assumptions.
- Rehearse coping with difficult situations.

Psychotherapy10
- Cognitive therapy alone is better than no therapy and may be better than antidepressants alone.
- Cognitive therapy is equivalent to behavioral therapy, but superior to psychodynamic therapy, interpersonal therapy, and supportive therapy.
Psychotherapy plus antidepressant medication is probably better than either alone.

Referral to a mental health specialist
- Referral should be considered for any patient with major depression desiring cognitive or behavioral therapy.
- Consider referral for patients without treatment response on single agents. These patients may benefit from change to other agents in the same or other classes, addition of mood stabilizing agents, or electroconvulsive therapy for severe refractory depression or depression with psychotic features.

The anxiety disorders
Introduction
- Primary care physicians should be able to recognize and treat basic anxiety disorders. Among the DSM-IV anxiety disorders are generalized anxiety disorder, anxiety due to a general medical condition, panic disorder with and without agoraphobia, and substance induced anxiety disorder.
- Anxiety disorders best referred to a psychiatrist include agoraphobia without panic disorder, specific and social phobias, obsessive compulsive disorder, post-traumatic stress disorder, and acute stress disorder.
- Anxiety may present as insomnia, headaches, chronic fears, musculoskeletal pain, or gastrointestinal disturbance.

Generalized anxiety disorder (GAD)
Epidemiology
- The lifetime prevalence of GAD is 5.1%. The one year prevalence is 3.1%. 1
- Women are affected approximately 1.9 times as often as men. 1
- GAD is frequently associated with mood disorders, other anxiety disorders, and substance abuse.

Treatment
- Initial therapy may consist of 2–6 weeks of a benzodiazepine or several months of buspirone.
- Antidepressants require 3–4 weeks of therapy prior to onset of action. If used, they are often initially paired with a benzodiazepine.
- Cognitive therapy is also an effective treatment for GAD; it may be better than pharmacotherapy. The combination of cognitive therapy and medication improves outcome compared to treatment with medication alone. 11
- There is no well designed study of the long term treatment of GAD. 12

Benzodiazepines
- Benzodiazepines are very effective, but long term use carries the risk of dependence and occasionally addiction.
- The longer acting agents are least likely to cause dependence. These include chlordiazepoxide, diazepam, and flurazepam.

effects of cognitive therapy in depressed patients. J Affective Dis 1998;49:59–72. Reviewed 48 trials. The statistical methods used allow for a qualitative distinction between treatment groups, but do not provide information to describe the magnitude of difference between treatments in clinical terms. Not all trials used intention to treat analyses, the trials were small in size (approximately 40 patients in each), and only tricyclic antidepressants were studied.

The etymology of “anxiety”
The term stems from the Greek angko (ἀγκο): “to squeeze, embrace, or throttle”. The meaning evolved to “weight down with grief, burdens, trouble”, and concurrently to the Latin anxietas “troubled in mind”.


DSM-IV criteria for generalized anxiety disorder
A. There must have been a period of at least six months with prominent tension, worry and feelings of apprehension about everyday events and problems.
B. At least four of the symptoms listed below must be present, and at least one must be from group 1.
1. Autonomic arousal symptoms: palpitations; sweating; trembling or shaking; dry mouth.
2. Symptoms involving chest and abdomen: difficulty breathing; feeling of choking; chest pain or discomfort; nausea or abdominal distress.
3. Symptoms involving mental state: feeling dizzy or light-headed; derealization; depersonalization; fear of losing control or going crazy; fear of dying.
4. General symptoms: hot flushes or cold chills; numbness or tingling sensations. Continued
Side effects include sedation, impairment of performance, transient anterograde amnesia, disinhibition, and depression.

These agents should be used with caution in patients with a history of substance abuse because of the risk of CNS depression and addiction.

Withdrawal seizures are most likely with short acting benzodiazepines.

Benzodiazepines rarely cause fatal overdose when taken alone, but when combined with other CNS depressants, they can be lethal.

**Buspirone**
- Among patients with GAD taking buspirone, 54% had significant clinical improvement, compared to 28% of patients on placebo.\(^{13}\)
- Buspirone and benzodiazepines have similar efficacy.\(^{14}\)
- It is only effective if taken regularly.
- Side effects (headache, nausea, and dizziness) are mild and infrequent. Unlike benzodiazepines, it does not cause impairment of memory, cognitive performance, or driving skills. It has no sedative hypnotic effects.
- It has no potential for dependence, withdrawal symptoms, or rebound anxiety after drug withdrawal.
- In one observational study, it was shown to be safe to use for up to one year.\(^{15}\)
- There is probably less relapse after buspirone treatment than after treatment with benzodiazepines.

**Buspirone v Benzodiazepines v Placebo for Anxiety over Four Weeks: Hamilton Anxiety Scale (HAM-A) Ratings**\(^{14}\)

<table>
<thead>
<tr>
<th>HAM-A total score</th>
<th>Week 0</th>
<th>Week 2</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buspirone</td>
<td>24.5</td>
<td>14.3</td>
<td>12.1</td>
</tr>
<tr>
<td>Diazepam</td>
<td>25.5</td>
<td>13.5</td>
<td>13.3</td>
</tr>
<tr>
<td>Placebo</td>
<td>24.5</td>
<td>18.9</td>
<td>17.2</td>
</tr>
</tbody>
</table>

**Antidepressants**
Several studies have shown benefit with antidepressants, particularly imipramine, in generalized anxiety disorder. While benzodiazepines provide greater relief of symptoms during the first two weeks of study, antidepressants show equal or better relief thereafter.

**Antidepressants v Benzodiazepines v Placebo for Anxiety Over Eight Weeks: Hamilton Anxiety Scale Ratings (HAM-A)**\(^{16}\)

<table>
<thead>
<tr>
<th>HAM-A psychic score</th>
<th>Week 1</th>
<th>Week 4</th>
<th>Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipramine</td>
<td>21.1</td>
<td>12.7</td>
<td>10.8</td>
</tr>
<tr>
<td>Trazodone</td>
<td>21.4</td>
<td>14.3</td>
<td>12.9</td>
</tr>
<tr>
<td>Diazepam</td>
<td>17.5</td>
<td>14.0</td>
<td>13.0</td>
</tr>
<tr>
<td>Placebo</td>
<td>21.7</td>
<td>18.5</td>
<td>16.0</td>
</tr>
</tbody>
</table>

5. Symptoms of tension: muscle tension or aches and pain; restlessness and inability to relax; feeling keyed up, on edge, or mentally tense; a sensation of a lump in the throat or difficulty in swallowing.

6. Other non-specific symptoms: exaggerated response to minor surprises; difficulty in concentrating because of worrying; persistent irritability; difficulty in getting to sleep because of worrying.

C. The patient does not meet the criteria for panic disorder, phobic anxiety disorder, obsessive compulsive disorder, or hypochondriacal disorder.

D. The anxiety is not due to a physical disorder, an organic mental disorder, or a psychoactive substance related disorder.


The Hamilton Anxiety Scale
This scale, often used in clinical trials, contains 14 symptoms (seven psychic and seven somatic), each rated from 0 to 4 points for severity. The maximum score for the psychic and somatic sections is 28 each, and the maximum combined score is 56. The average person has a total score of less than 5; a score of 15 represents clinically significant anxiety.

\(^{16}\) Rickels K, Downing R, Schweizer E, Hassman H. Antidepressants for the Continued
Botanicals: kava extract

- Kava extract is superior to placebo for the treatment of anxiety; it lowers anxiety by a mean of 10 points more than placebo on the HAM-A scale.\(^\text{17}\)

Referral to a psychiatrist, psychologist, or therapist

- Consider referral for any patient who wants cognitive therapy.
- Patients refractory to medical therapy or with recurrent relapse after withdrawal of therapy should be referred to a psychiatrist.

Panic disorder

**Epidemiology**

- The lifetime risk of having an isolated panic attack is 7.2%.\(^\text{18}\)
- The lifetime and one year prevalence of panic disorder are 3.5%, and 2.3% respectively.\(^\text{1}\)
- The lifetime risk is approximately 2.5 times greater in women.\(^\text{1}\)
- In primary care settings, the prevalence is 6.5–19%.\(^\text{19}\)
- Up to 25% of first degree relatives of patients with panic disorder have the disorder themselves.\(^\text{19}\)
- The prevalence of panic disorder in patients with chest pain who have a normal coronary angiogram is 33–43%.\(^\text{19}\)
- The rate of suicide attempts in patients with panic disorder is 7%; with panic disorder and depression the rate is 20%.\(^\text{19}\)

**Diagnosis**

- Onset is generally between ages 15 and 30.
- Patients must experience four panic attacks in one month or one attack with persistent fear.
- Panic disorder is easily missed. The average panic disorder patient sees 10 physicians before being diagnosed. This may be due to the often misleading presentation of anxiety disorder: chest pain, shortness of breath, gastrointestinal symptoms, neurologic symptoms.\(^\text{19}\)
- Common comorbidities include major depression, agoraphobia, and substance abuse. Depression coexists in over 50% of patients with panic attack or panic disorder.\(^\text{18}\)
- Rule out other medical disorders, intoxication, withdrawal syndromes, caffeine use, and complications of medication use.

**Treatment**

- Panic disorder is highly treatable; up to 85% of patients who complete a combination of medication and psychotherapy will improve.
- Patient education regarding the diagnosis and its implications is crucial, since many patients feel as if they’re

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**DSM-IV criteria for panic disorder**

- **Panic attack** is described as a sudden discrete period (usually 5–30 minutes) of intense fear or discomfort accompanied by at least four symptoms from groups 1–4 of the GAD symptoms. At least one symptom must be from group 1.
- **Panic disorder** is the presence of recurrent unexpected panic attacks followed by at least one month of persistent concern about having another panic attack, worry about the possible implications or consequences of the panic attacks (anticipatory anxiety), or significant behavioral change related to the attacks (including agoraphobia or social phobia).

**The panics of Charles Darwin**

At the age of 28 Darwin noted “I have awakened in the night being slightly so unwell and felt so much afraid though my reason was laughing and told me there was nothing”. Barloon TJ, Noyes R Jr. Charles Darwin and panic disorder. JAMA 1997;277:138–41.

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going to die during an attack and are concerned that they have a serious medical disorder.

Psychotherapy
- Cognitive behavioral therapy is equivalent to pharmacotherapy and may be more efficacious for relapse prevention. After therapy is finished, the patient can continue to use the techniques and concepts they have integrated to prevent symptoms; patients who have finished pharmacotherapy do not have this resource.
- A combination of therapy and medication is probably better than medication alone.

Panic Disorder Treated with Cognitive Behavioral Therapy (CBT) and/or Antidepressants: Response Rates

<table>
<thead>
<tr>
<th></th>
<th>Benzo/Diazepines</th>
<th>CBT alone</th>
<th>CBT and imipramine</th>
<th>Imipramine alone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of patients maintaining 40% reduction in symptoms (%)</td>
<td>57</td>
<td>47</td>
<td>38</td>
<td>36</td>
<td>26</td>
</tr>
<tr>
<td>Dropout rate in each phase (%)</td>
<td>10</td>
<td>17</td>
<td>17</td>
<td>25</td>
<td>67</td>
</tr>
</tbody>
</table>

Pharmacotherapy
For a complete discussion of these medications, see the sections on depression and GAD.
- SSRIs, TCAs, venlafaxine, nafazodone, and benzodiazepines (alprazolam and clonazepam) are all effective treatments. Alprazolam is short acting and therefore may cause rebound anxiety between doses. It also causes drug dependence more often than clonazepam.
- SSRIs and TCAs may take 3–6 weeks to induce a response.
- Benzodiazepines are immediately effective in treating anticipatory anxiety and phobic avoidance. Drawbacks include many side effects and the potential for dependence and abuse.
- It may be reasonable to give 4–6 weeks of a benzodiazepine until the patient shows an adequate response to an antidepressant agent.
- Medication should continue for at least six months of treatment before a taper is attempted.


Barlow DH, Gorman J, Shear MK, Woods S. Cognitive-behavioral therapy, imipramine, or their combination for panic disorder: a randomized controlled trial. JAMA 2000;283:2529–36. Double blind RCT of 312 patients. The acute phase consisted of eleven 50 minute therapy sessions and/or 30 minute long drug treatment sessions over 12 weeks. The maintenance phase included only treatment responders; they had similar sessions every month for six months. Differences between CBT and imipramine were not statistically significant. All differences with placebo were statistically significant.

Elements of cognitive behavioral therapy for panic disorder
- Patient education
- Monitoring of panic symptoms
- Breathing techniques
- Cognitive change of catastrophic thoughts associated with panic attacks
- Exposure and desensitization to somatic fear cues

DEPRESSION, ANXIETY, AND SOMATIZATION
TCAs, SSRIs, and Placebo in the Treatment of Panic Disorder (percentage of patients with no further full panic attacks)

<table>
<thead>
<tr>
<th>Week of follow-up</th>
<th>Agent</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clomipramine</td>
<td>8%</td>
<td>30%</td>
<td>37%</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>Paroxetine</td>
<td>8%</td>
<td>36%</td>
<td>51%</td>
<td>51%</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>8%</td>
<td>24%</td>
<td>32%</td>
<td>33%</td>
</tr>
</tbody>
</table>

*P ≤ 0.05 for drug v placebo

In two additional years of follow up, a total of 85% of paroxetine patients achieved success, compared to 72% of clomipramine patients and 59% of placebo patients.21,22

Somatization

Introduction23,24

Somatization is the presence of multiple somatic symptoms without medical explanation. It is unclear if somatization is a discrete disease, an epiphenomenon of other psychiatric illnesses, or a normal dimension of experience that appears pathological. Explanations include:

- **transduction**: the theory that unexpressed emotions are transduced into bodily sensations via unconscious mechanisms
- **an anthropologic/behavioral model**: patients choose to present somatic symptoms rather than psychological symptoms, as this is more socially acceptable
- **a reductionist model**: like all other disease, somatization is the result of a biologic process occurring at the cellular and molecular level.

Epidemiology23,25

- Fifteen percent of primary care patients present with ≥ 5 medically non-explained symptoms.
- There is a strong association between the presence of medically non-explained symptoms and psychiatric illness.
- Patients with medically non-explained symptoms tend to be female, younger, to drink more alcohol, and to have greater social disability than those with medically explained symptoms.

Prevalence of Psychiatric Illness among Patients with Medically Non-Explained Symptoms25

<table>
<thead>
<tr>
<th>Number of symptoms</th>
<th>Prevalence of psychiatric illness (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>1–4</td>
<td>18</td>
</tr>
<tr>
<td>≥ 5</td>
<td>69</td>
</tr>
</tbody>
</table>

- Patients with chronic unexplained symptoms are frequently difficult and frustrating to care for. Such patients may be the greatest single challenge a physician faces.

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22. Lecrubier Y, Judge R and the Collaborative Paroxetine Panic Study Investigators. Long-term evaluation of paroxetine, clomipramine and placebo in panic disorder. Acta Psychiatr Scand 1997;95:153–60. Included patients from the above study who completed the 12 week course of therapy and elected to continue receiving their randomized treatments (i.e. a self-selected group).

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DSM-IV criteria: somatization disorder

A. A history of many physical complaints beginning before age 30 that occur over a period of several years and result in treatment being sought or significant impairment in social, occupational, or other important areas of functioning.

B. Each of the following criteria must have been met, with individual symptoms occurring at any time during the course of the disturbance.

1. *Four pain symptoms*: a history of pain related to at least four different sites or activities.
2. *Two gastrointestinal symptoms*: a history of at least two GI symptoms other than pain.

Continued
Diagnosis

- Most patients with several non-medically explained symptoms will not fit neatly into standard definitions of somatization disorder.
- Somatic symptoms may appear exaggerated, contradictory, or unusual. The patient often uses dramatic expressions to describe their pain. Symptoms are often related to life stressors.
- These patients report excessive concern about their health which is not relieved by physician reassurance or negative diagnostic tests.
- Somatizing patients frequently have comorbid psychiatric disorders: major depression, dysthymia, GAD, panic disorder, and hypochondriasis.
- There is a history of care by multiple physicians that has been unsatisfactory.
- Patients often have poor social and occupational functioning.
- There is conscious or unconscious gain from illness.
- Response to medical treatment tends to be poor.

Treatment

- Establish a trusting, caring relationship. Tell the patient that you may not cure the problem but will work on it and will never dismiss the patient from your care.
- Legitimize the patient’s symptoms; do not dispute the reality of the complaints. Avoid the temptation to prematurely attribute symptoms to stress. It is helpful to use biological explanations for their symptoms, in particular to describe the model of neurotransmitters as mediators of pain.
- Use restraint in ordering diagnostic tests.
- Refer to specialists only when appropriate and continue to see the patient regularly.
- Clarify treatment goals. Aim for minimizing or learning to live with symptoms rather than for cure.
- Arrange regularly scheduled follow-up visits at 1–4 week intervals. Discourage walk-in visits.
- A trial of antidepressants may be beneficial for treatment of pain symptoms.
- Cognitive behavioral therapy may be of benefit. Patients who receive CBT have medically unexplained symptoms approximately 32–35% as often as patients who do not get therapy, when measured 6–12 months after therapy.

3. One sexual symptom: a history of at least one sexual or reproductive symptom other than pain.
4. One pseudoneurological symptom: a history of at least one symptom or deficit suggesting a neurological condition not limited to pain.

C. Either (1) or (2).
1. After appropriate investigation, each of the symptoms in criterion B cannot be fully explained by a known general medical condition or the direct effects of a substance (for example, alcohol).
2. When there is a related general medical condition, the physical complaints or resulting social or occupational impairment are in excess of what would be expected from the history, physical examination, or laboratory findings.
3. The symptoms are not intentionally feigned or produced (as in factitious disorder or malingering).

A thorough search of Medline and Embase, using the keywords “somatization”, “somatoform”, “Briquet’s syndrome”, “polymorphous pain”, and “psychosomatic”, uncovered no medical or psychiatric society based guidelines for the management of patients with somatization. The recommendations to the left are based on expert opinion.

A meta-analysis of 11 RCTs of patients with somatoform pain. Treatment with antidepressants reduced pain more than treatment with placebo.

## Table 12.1 Drugs for depression, anxiety, and somatization.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage forms</th>
<th>Usual dose</th>
<th>Dose range</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SSRIs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine (Prozac)</td>
<td>10/20 mg tabs, 20mg/5ml liquid</td>
<td>20 mg qd</td>
<td>5–80 mg qd</td>
<td>Most common side effects: diarrhea, headache, nausea, insomnia, anxiety, decreased libido, delayed ejaculation, anorgasmia. Give 1/2 lowest usual dose for 7 days, then titrate up to usual dose.</td>
</tr>
<tr>
<td>Sertraline (Zoloft)</td>
<td>50/100 mg tabs</td>
<td>100–150 mg qd</td>
<td>50–200 mg qd</td>
<td></td>
</tr>
<tr>
<td>Paroxetine (Paxil)</td>
<td>20/30 mg tabs</td>
<td>20 mg qd</td>
<td>10–50 mg qd</td>
<td></td>
</tr>
<tr>
<td>Citalopram (Celexa)</td>
<td>20/40 mg tabs</td>
<td>20–40 mg qd</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TCAs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary amines</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desipramine (Norpramin)</td>
<td>10/25/50/75, 100/150 mg</td>
<td>150–200 mg qHS</td>
<td>25–300 mg qHS</td>
<td>Start at a low dose and titrate until therapeutic range achieved. Increase q 4 weeks. Less sedating than tertiary amines. Common side effects: blurred vision, constipation, dizziness, dry mouth, tremors, and urinary disturbance.</td>
</tr>
<tr>
<td>Nortriptyline (Pamelor)</td>
<td>10mg/5ml liquid, 10/25/50/75 mg tabs</td>
<td>75–100 mg qHS</td>
<td>25–150 mg qHS</td>
<td></td>
</tr>
<tr>
<td><strong>Tertiary Amines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imipramine (Tofranil)</td>
<td>10/25/50/75, 100/125/150 mg tabs</td>
<td>150–200 mg qHS</td>
<td>50–300 mg qHS</td>
<td>Start at a low dose and titrate until therapeutic range achieved. Increase q 4 weeks. More sedating than secondary amines. Side effects: blurred vision, constipation, dry mouth, dizziness, tremors, and urinary disturbance.</td>
</tr>
<tr>
<td>Amitriptyline (Elavil)</td>
<td>10/25/50/75, 100/150 mg tabs</td>
<td>150–200 mg qHS</td>
<td>50–300 mg qHS</td>
<td></td>
</tr>
<tr>
<td>Doxepin (Adapin, Sinequan)</td>
<td>10mg/ml liquid, 10/25/50/75, 100/150 mg tabs</td>
<td>150–200 mg qHS</td>
<td>25–300 mg qHS</td>
<td></td>
</tr>
<tr>
<td><strong>Other antidepressants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion (Wellbutrin)</td>
<td>75/100 mg tabs</td>
<td>100 bid × 7d, then 100–150mg tid</td>
<td></td>
<td>Side effects: anxiety, restlessness, insomnia. Does not cause sexual dysfunction. The incidence of seizures is 0.4%, slightly higher than with other antidepressants.</td>
</tr>
<tr>
<td>(Wellbutrin SR)</td>
<td>100/150 mg tabs</td>
<td>150 qd × 7d, then 150–200 mg bid</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 12.1 Continued

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage forms</th>
<th>Usual dose</th>
<th>Dose range</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venlafaxine (Effexor)</td>
<td>25/37.5/50/75/100 mg tabs</td>
<td>75–225mg qd Divide into a bid schedule</td>
<td>75–450 mg qd</td>
<td>Same side effects as SSRIs. May also cause sedation, sweating, and, at high doses, increased blood pressure. XR preparation is taken once per day.</td>
</tr>
<tr>
<td>(Effexor XR)</td>
<td>37.5/75/100 mg tabs</td>
<td>75–225mg daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trazodone (Desyrel)</td>
<td>50/100/150/300 mg tabs</td>
<td>200–300 qHS</td>
<td>30–600 mg qd</td>
<td>Dosage for depression. Dosage for insomnia. Side effects: sedation, orthostatic hypotension, nausea, emesis.</td>
</tr>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alprazolam (Xanax)</td>
<td>0.25/0.5/1/2 mg tabs</td>
<td>0.25–1.5 tid</td>
<td>0.75–4.5 mg qd</td>
<td>Elimination half-life: 6–20 hours. Alprazolam 0.5 mg PO is equivalent in potency to lorazepam 1 mg.</td>
</tr>
<tr>
<td>Lorazepam (Ativan)</td>
<td>0.5/1/2 mg tabs</td>
<td>1 bid–2 tid</td>
<td>2–6 mg qd</td>
<td>Elimination half-life: 10–20 hours.</td>
</tr>
<tr>
<td>Diazepam (Valium)</td>
<td>2/5/10 mg tabs</td>
<td>2 bid–10 qid</td>
<td>4–40 mg qd</td>
<td>Rapid onset of action. Elimination half-life is 30–100 hours. Diazepam 5 mg PO is equivalent in potency to lorazepam 1mg.</td>
</tr>
<tr>
<td>Chlordiazepoxide (Librium)</td>
<td>5/10/25 mg tabs</td>
<td>5 tid–10 qid</td>
<td>15–100 mg qd</td>
<td>Elimination half-life is 30–100 hours. Chlordiazepoxide 10 mg is equivalent in potency to 1 mg lorazepam.</td>
</tr>
<tr>
<td>Clonazepam (Klonopin)</td>
<td>0.5/1/2 mg tabs</td>
<td>0.25–2 tid</td>
<td>1.5–20 mg qd</td>
<td>Elimination half-life is 18–50 hours. Clonazepam 0.25 mg is equivalent in potency to 1 mg lorazepam.</td>
</tr>
<tr>
<td><strong>Other Anxiolytics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buspirone (Buspar)</td>
<td>5/10/15 mg tabs</td>
<td>5–10 tid</td>
<td>5–60 mg qd</td>
<td>Does not cause sedation, may cause restlessness. Headache, GI side effects and dizziness occur rarely. Not highly toxic in overdose.</td>
</tr>
</tbody>
</table>

13 Dermatologic disease
Xiomara Ramírez-Ortega

Introduction
Epidemiology

Prevalence of Skin Diseases (per 1000 US Population)†

<table>
<thead>
<tr>
<th>Disease</th>
<th>18–24</th>
<th>25–34</th>
<th>35–44</th>
<th>45–54</th>
<th>55–64</th>
<th>65–74</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatophytosis</td>
<td>62</td>
<td>88</td>
<td>122</td>
<td>156</td>
<td>151</td>
<td>127</td>
</tr>
<tr>
<td>Acne vulgaris</td>
<td>172</td>
<td>83</td>
<td>25</td>
<td>8</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Seborrheic dermatitis</td>
<td>38</td>
<td>41</td>
<td>41</td>
<td>31</td>
<td>28</td>
<td>36</td>
</tr>
<tr>
<td>All eczema/dermatitis</td>
<td>15</td>
<td>28</td>
<td>15</td>
<td>14</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>Contact dermatitis</td>
<td>14</td>
<td>10</td>
<td>17</td>
<td>17</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>5</td>
<td>6</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Malignant tumors</td>
<td>0.1</td>
<td>0.1</td>
<td>3</td>
<td>10</td>
<td>19</td>
<td>36</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>2</td>
<td>6</td>
<td>5</td>
<td>11</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>≥ 1 skin disease</td>
<td>365</td>
<td>318</td>
<td>328</td>
<td>357</td>
<td>361</td>
<td>410</td>
</tr>
</tbody>
</table>

History
Past medical history, medications, diet, occupation, exposure to personal or household cleaning agents, and sun exposure may all provide clues to the diagnosis.

Physical exam
- Examine hair, nails, and mucous membranes, in addition to area of concern.
- Describe shape, size, texture, color, arrangement, and distribution of skin changes. See Table 13.1 for dermatologic terminology.
- Visual pattern recognition is critical in dermatology. The symbols † and †† denote full text articles with color photographs that can be found in the OVID database.

Acne vulgaris†
Clinical presentation
- Usually occurs in adolescence and is more severe in males.
- Manifests as closed comedones (whiteheads), open comedones (blackheads), papules, nodules, cysts, or papulopustules. It occurs most often on the face, upper aspect of the arms, and the trunk.
- Exogenous or endogenous corticosteroids, lithium, phenytoin, high doses of B vitamins, and emotional stress can cause exacerbations. A common misconception is an association with any kind of food.
- May result in pitted or hypertrophic scars.

Treatment
The use of cosmetics should be discouraged. Topical agents should be applied after washing when the skin is completely dry.
Mild disease

- Topical benzoyl peroxide or other over the counter keratolytics such as a salicylic acid preparation.

Moderate and severe disease

- Combination therapy with two or three agents provides better outcome than one agent alone.\(^2,3\)
- Useful agents include tretinoin, topical antibiotics (erythromycin or clindamycin), benzoyl peroxide, and topical adapalene.
- Consider oral antibiotics (tetracycline, erythromycin) if too much of the body surface area is affected to cover with topical agents.
- Allow six weeks of therapy for improvement.

Nodulocystic acne or treatment resistant acne

- These patients should be referred to a dermatologist for possible isotretinoin therapy.

\(^2\) Lookingbill DP, Chalker DK, Lindholm JS et al. Treatment of acne with a combination clindamycin/benzoyl peroxide gel compared with clindamycin gel, benzoyl peroxide gel, and vehicle gel: combined results of two double blind investigations. J Am Acad Dermatol 1997;37:590–5. Randomized, double blind study of 393 patients. Only the 85% of patients who completed therapy were included in the final analysis.

### Table 13.1 Common terms used for description of dermatologic disease.

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
<th>Common and important examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulla</td>
<td>Superficial elevation of the skin filled with serous fluid and &gt; 5 mm in diameter</td>
<td>Bullous pemphigoid, pemphigus vulgaris, dermatitis herpetiformis</td>
</tr>
<tr>
<td>Comedone</td>
<td>Black or white appearing plugs of keratin in the openings of hair follicles</td>
<td>Acne vulgaris</td>
</tr>
<tr>
<td>Macule</td>
<td>A flat change in skin color that is (\leq 10) mm in diameter</td>
<td>Nevi, lentigo maligna, tinea versicolor, drug reaction, viral exanthem, secondary syphilis</td>
</tr>
<tr>
<td>Nevus</td>
<td>Benign tumor composed of cells derived from melanocytes</td>
<td></td>
</tr>
<tr>
<td>Nodule</td>
<td>A solid, elevated lesion, up to 2 cm in diameter with a palpable deep component</td>
<td>Melanoma, basal cell carcinoma, squamous cell carcinoma, furuncle, acne vulgaris, prurigo nodularis</td>
</tr>
<tr>
<td>Papule</td>
<td>A lesion that is elevated and (\leq 10) mm in diameter</td>
<td>Melanoma, arthropod bite, nevi, warts, seborrheic keratosis, drug reaction, viral exanthem, secondary syphilis</td>
</tr>
<tr>
<td>Patch</td>
<td>A flat change in skin color that is &gt; 10 mm in diameter</td>
<td>Nevi, vitiligo, melasma, drug reaction, Lyme disease (erythema migrans)</td>
</tr>
<tr>
<td>Plaque</td>
<td>A lesion that is elevated and &gt; 10 mm in diameter</td>
<td>Psoriasis, eczema, seborrheic dermatitis</td>
</tr>
<tr>
<td>Pustule</td>
<td>A circumscribed, compressible, elevated lesion that contains pus</td>
<td>Acne vulgaris, folliculitis, acute dermatitis, pustular psoriasis</td>
</tr>
<tr>
<td>Vesicle</td>
<td>Superficial elevation of the skin filled with serous fluid and (\leq 5) mm in diameter</td>
<td>Herpes simplex, varicella (chickenpox), herpes zoster (shingles), acute eczema</td>
</tr>
</tbody>
</table>
Skin cancer†
Precursor lesions
Actinic keratosis (solar keratosis)††
Presentation
● These precursor lesions require years of sun exposure to develop and may transform into squamous cell carcinoma (SCC) or basal cell carcinoma.
● They occur more commonly in light skinned people and more frequently with age.
● They are scaly, erythematous lesions with a rough texture that occur most commonly on the face, the dorsum of hands, and on the scalp in bald people.
● Approximately 26% of lesions spontaneously remit each year. During this period, 44% of people will develop new lesions.
● Approximately 0.1% of keratoses convert to squamous cell carcinoma each year. This low yearly transformation rate for single lesions can mean a substantial lifetime risk of transformation for patients with several actinic keratoses. The conversion rate to basal cell carcinoma is not defined.

Treatment
● UV A and B sun screen increases the remission rate and lowers the rate of formation of new lesions.
● Tretinoin 0.05–0.1% cream is useful for mild actinic damage.
● Referral to a dermatologist should be considered for thick lesions, lesions with “horns”, or ulcerated lesions. These may be malignant. Also consider referral for patients with multiple lesions.
● In patients with a history of non-melanoma skin cancer, a low fat diet may reduce the incidence of actinic keratosis. Patients on a low fat diet develop three new keratoses over 24 months, compared to 10 new keratoses on a regular diet (P < 0.001).

Dysplastic nevi (atypical moles)†
Epidemiology
● These are pigmented lesions not present at birth that develop atypical features over time. They can be inherited or sporadic.
● The prevalence of dysplastic nevi is 2–18%.
● Among white patients with dysplastic nevi, the lifetime risk of cutaneous melanoma is approximately 10% (the risk of melanoma in people without dysplastic nevi is approximately 0.6%).
● The prevalence of melanoma rises at a steady rate after age 10 for people with dysplastic nevi who are from melanoma prone families (two or more first degree relatives having cutaneous melanoma). The cumulative lifetime risk of melanoma for these patients is > 80%.

Presentation
● Pigmented – the color is usually variable within the same lesion.
• Single or multiple and occur at any site.
• Usually > 6 mm, often > 10 mm.
• Usually round or oval with irregular or indistinct borders.
• Patients may have a few to more than 100.
• May be sporadic or familial.
• Usually appear before age 20, but can occur throughout life.

Treatment
• Patients should be taught self examination to detect any changes in nevi.
• Periodic physician examination of the eyes, scalp, and the entire surface of the skin. For those with a family history of dysplastic nevi, follow up should be every 3–6 months.
• At least one of the more atypical lesions should be biopsied.
• Changing lesions or atypical lesions difficult to differentiate from early melanoma should be excised.
• Patients should avoid sun exposure and use sun screen.

Congenital nevi
• These are melanocytic nevi present since birth. They occur in approximately 1% of all newborns, but most of these are small.
• They may have an irregular surface, hypertrichosis, and increased pigmentation with color shading variable in the same lesion.
• The lifetime risk of melanoma in patients with large congenital nevi (> 20 cm in diameter) is approximately 5–20%.8

Lentigo maligna
• An irregular melanotic macular lesion occurring on sun exposed areas in middle aged to elderly patients.
• They are very slow growing, but if untreated may progress to lentigo maligna melanoma.

Non-melanoma skin cancer
Basal cell carcinoma (BCC)†
• This is the most common type of skin cancer.
• It advances by direct extension, destroying normal tissue, but rarely metastasizes.
• Most occur on the head (85%); 25–30% occur on the nose alone.

Epidemiology
• Risk factors are fair skin and degree of sun exposure.
• Incidence increases markedly after age 40.
• In the US, lifetime risk for white men and women is 33–39% and 23–28% respectively.9
• The case fatality rate for BCC is approximately 1 in 2000.10

Categories
• Noduloulcerative (most common): translucent, skin colored, waxy papules with telangiectasias. It enlarges slowly and the central area becomes depressed. Can ulcerate.


• *Pigmented:* similar to noduloulcerative, except brown, blue, or black. It can resemble melanoma.

• *Morphea like/sclerosing:* solitary, flat, or slightly depressed whitish, sclerotic plaque. The surface is smooth and shiny. The borders of the lesion are often ill defined.

• *Superficial:* erythematous, scaly, slightly infiltrated patch, commonly occurring on the trunk. It may be surrounded by a fine, pearly border. Can resemble psoriasis, eczema, or tinea corporis.

**Squamous cell carcinoma (SCC)**

*Epidemiology*

- Risk factors are fair skin, sun exposure, and immunosuppression.
- The US lifetime risk for white men and women is 9–14% and 4–9%, respectively.9
- The case fatality rate for SCC is approximately 7 per 1000.10

*Presentation*

- Can develop as a firm papule or nodule with an indurated base.
- Crusting or ulceration can develop; patients may present with a shallow ulcer surrounded by an elevated indurated border. The ulcer is often covered by crust with a red, granular base.
- SCCs most commonly occur on the sun damaged skin of the head, neck, and dorsum of the hands.
- SCC in areas of actinically damaged skin is less aggressive and less likely to metastasize than at other sites.

**Odds Ratios for Local Recurrence and Metastasis of SCC**11

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Local recurrence</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter: ≥ 2 cm v &lt; 2 cm</td>
<td>2.2</td>
<td>4.3</td>
</tr>
<tr>
<td>Tumor depth: ≥ 4 mm v &lt; 4 mm</td>
<td>3.7</td>
<td>11.7</td>
</tr>
<tr>
<td>Poorly v well differentiated</td>
<td>2.5</td>
<td>4.8</td>
</tr>
<tr>
<td>Lip tumor v other sun exposed skin</td>
<td>1.3</td>
<td>2.9</td>
</tr>
<tr>
<td>Scar carcinoma v sun exposed skin</td>
<td>–</td>
<td>11.1</td>
</tr>
</tbody>
</table>

*Treatment*

- Refer to a dermatologist for incisional or excisional biopsy.
- These patients should avoid prolonged sun exposure and use sunscreen appropriately.
- Thorough physical exam and follow up screening for new primary tumors and recurrences may be beneficial.

**Cutaneous melanoma†**

*Epidemiology*

- The lifetime risk for white Americans was 1/123 in 1987, 1/87 in 1996, and is expected to reach 1/75 during the year 2000.
- Represents 4% of new cancers in men and 3% in women.


† Rose DE, Carroll JR, Day CL. Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip: implications for treatment modality selection. J Am Acad Dermatol 1992;26:976–90. Pooling of data from 71 retrospective studies. In studies following patients for more than five years, the rate of local recurrence was 30.3% and the rate of metastasis was 5.2%.


**Risk Factors for Melanoma**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changing mole</td>
<td>Very high</td>
</tr>
<tr>
<td>Atypical mole(s) and familial melanoma</td>
<td>148</td>
</tr>
<tr>
<td>Atypical mole(s) but no familial melanoma</td>
<td>27</td>
</tr>
<tr>
<td>Congenital mole</td>
<td>21</td>
</tr>
<tr>
<td>White race (v black)</td>
<td>12</td>
</tr>
<tr>
<td>Family history melanoma</td>
<td>8</td>
</tr>
<tr>
<td>Sun sensitivity</td>
<td>3</td>
</tr>
<tr>
<td>Excessive sun exposure</td>
<td>3</td>
</tr>
</tbody>
</table>

### Table 13.2 Drugs for dermatologic disease.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage forms</th>
<th>Usual dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-acne medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adapalene gel/soln</td>
<td>0.1%</td>
<td>qHS</td>
<td>May irritate the skin</td>
</tr>
<tr>
<td>Benzoyl Peroxide gel, cream</td>
<td>2.5/5/10%</td>
<td>qod-bid</td>
<td>May bleach hair or fabric. Avoid lotion pre pregnancy and during pregnancy</td>
</tr>
<tr>
<td>Clindamycin soln (Cleocin-T)</td>
<td>1%</td>
<td>bid</td>
<td>Titrate: irritation vs benefit</td>
</tr>
<tr>
<td>Erythromycin soln</td>
<td>2%</td>
<td>bid</td>
<td></td>
</tr>
<tr>
<td>Salicylic acid pads (Stridex pads)</td>
<td>2%</td>
<td>bid</td>
<td></td>
</tr>
<tr>
<td>Tretinoin gel (Retin-A)</td>
<td>0.01/0.025%</td>
<td>qod-bid</td>
<td>Titrate: irritation vs benefit</td>
</tr>
<tr>
<td>Tretinoin cream (Retin-A)</td>
<td>0.025/0.05/0.1%</td>
<td>qod-bid</td>
<td></td>
</tr>
<tr>
<td><strong>Topical azole antifungals</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clotrimazole cream (Lotrimin)</td>
<td>1%</td>
<td>qd-bid × 4 weeks</td>
<td></td>
</tr>
<tr>
<td>Econazole cream (Spectazole)</td>
<td>1%</td>
<td>qd-bid × 4 weeks</td>
<td></td>
</tr>
<tr>
<td><strong>Topical allylamine antifungals</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Terbinafine cream (Lamisil)</td>
<td>1%</td>
<td>qd-bid × 4 weeks</td>
<td></td>
</tr>
<tr>
<td><strong>Other topical antifungals</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tolnaftate (Tinactin)</td>
<td>1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciclopiroxolamine (Loprox)</td>
<td>1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Oral antifungals</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itraconazole (Sporanox)</td>
<td>100 mg/200 mg</td>
<td>200 mg PO qd</td>
<td>For tinea unguium: 3 months. Follow LFTs in patients with liver disease.</td>
</tr>
<tr>
<td>Terbinafine (Lamisil)</td>
<td>250 mg</td>
<td>250 mg PO qd</td>
<td>For tinea unguium: 3–4 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>250 mg PO qd</td>
<td>For tinea pedis: 2 weeks Check LFTs at approximately 4 weeks.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Avoid in patients with pre-existing liver or kidney disease.</td>
</tr>
<tr>
<td><strong>Agents specific for psoriasis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcipotriene cream (Donovex)</td>
<td>0.05%</td>
<td>Apply bid</td>
<td>Use ≤ 100 mg/day. Local irritation is common (20%). Use with caution in</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>intertriginous areas or face. For patients with kidney stones or renal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>failure, follow serum calcium.</td>
</tr>
<tr>
<td>Tazarotene (Tazorac) gel</td>
<td>0.05%/0.1%</td>
<td>Apply qHS</td>
<td>Apply to &lt;20% of body surface area. May cause irritation.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Whited J, Grichnick JM. Does this patient have a mole or a melanoma? The Rational Clinical Examination. JAMA 1998;279:696–701. Reviewed two studies of dermatologists using the ABCD(E) checklist.

In the first study, 65 patients with melanoma were assessed. A positive test required the presence of at least one of the ABCD(E) criteria. The test was 92% sensitive. In the second study, six patients with melanoma and 186 controls were assessed. A positive test required that the B, C, and D criteria be present. The test was 100% sensitive and 98.4% specific.

**Table 13.2 Continued**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage forms</th>
<th>Usual dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Emollients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Petroleum jelly (Vaseline)</td>
<td></td>
<td></td>
<td>Most greasy, most effective</td>
</tr>
<tr>
<td>Keri lotion</td>
<td></td>
<td></td>
<td>Less greasy than petroleum jelly</td>
</tr>
<tr>
<td>Lac Hydrin 12% lotion</td>
<td></td>
<td></td>
<td>Less greasy than Keri lotion</td>
</tr>
<tr>
<td><strong>Coal tar preparations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coal tar extract (T Gel)</td>
<td>1%</td>
<td>5–10 min/day</td>
<td>May be irritating. After disease is controlled, apply 1 day/week. May be applied to face, body, or scalp.</td>
</tr>
<tr>
<td>Crude coal tar (Zetar)</td>
<td>2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coal tar soln (Denorex)</td>
<td>9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coal tar/salicylic acid (Sebutone)</td>
<td>0.5%/2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Agents specific for seborrheic dermatitis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketoconazole shampoo (Nizoral)</td>
<td>1%/2%</td>
<td>5–10 min/day</td>
<td>Wash off after 5–10 minutes. Later switch to biw</td>
</tr>
<tr>
<td>Ketoconazole cream (Nizoral)</td>
<td>2%</td>
<td>qd-bid</td>
<td>Only for the face or body, not the scalp.</td>
</tr>
<tr>
<td>Pyrithione zinc shampoo (Head and Shoulders)</td>
<td>1%/2.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selenium sulfide shampoo (Selsun)</td>
<td>1%/2.5%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Diagnosis**

Early detection
- For patients at increased risk of melanoma or presenting with a concerning mole, examination of the entire skin surface should be performed.
- The ABCD(E) checklist is useful for distinguishing nevi from melanomas; it is about 92% sensitive and 98% specific.\(^{12}\)

A Asymmetry: if the lesion is bisected, one half is not identical to the other half.
B Border irregularity: the border of the lesion is uneven or ragged, as opposed to smooth and straight.
C Color variegation: > 1 shade of pigment is present.
D Diameter of the lesion is \( \geq 6 \text{ mm} \).
E Elevation: elevation of the lesion above the surface
- Other risk factors distinguishing melanomas include pruritus, pain, increase in size, darkening, bleeding, or ulceration.
Classification

- **Superficial spreading melanoma**: its hallmark is the presence of various shades: browns, blacks, whites, grays, reds (although it may just be brown or black).
- **Acral lentiginous melanoma**: flat with irregular borders and black or dark brown in color. It is most common in blacks and Asians.
- **Lentigo maligna**: may have a complex pattern with highly irregular borders and bizarre shapes. They are brown-tan macules with variation in pigment pattern.
- **Nodular melanoma** can be a dome shaped, polypoid, or pedunculated nodule. It can arise in a nevus or normal skin. It is most commonly dark brown, red-brown, or black.

Evaluation and prognosis

- Patients suspected of cutaneous melanoma should have prompt subspecialist referral for assessment and possible punch, incisional, or excisional biopsy.
- **Clinical prognostic factors**: male sex and older age confer a worse prognosis. Extremity melanomas have a better outcome than trunk or scalp melanomas. Tumor thickness is the most important prognostic sign.\(^{14}\)

Steroid responsive dermatoses

**Rational use of corticosteroids**

**Vehicle and dressings**

- Potency and side effects of topical corticosteroids are increased by ointments or occlusive dressings (for example, with plastic wrap or hydrocolloid dressings).
- Lotions and creams are more cosmetically acceptable than ointments, but ointments are more soothing to dry skin than other preparations. Gels provide a drying effect for oily skin.

**Potency, classification, and dosage**

- **Classification**: topical corticosteroids have been ranked into seven classes based on an \textit{in vivo} vasoconstrictor assay. Class I is the most potent and class VII is the least potent. See Table 13.3 for specific agents.
  - Class I should only be used for very short periods on areas of lichenified skin and not on facial or intertriginous areas.
  - Class II should not be used for more than three weeks and not on facial or intertriginous areas.
  - Agents from other classes can be used for longer periods, but probably not for more than six weeks at a time without referral to a dermatologist.
- **Eczema**: for most diseases that end with the word \textit{dermatitis} or \textit{eczema}, class III–IV agents are used, except on the face, genitalia, and intertriginous areas. At these sites, use class VI–VII agents.

---


<table>
<thead>
<tr>
<th>Tumor thickness</th>
<th>5 yr survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.75 mm</td>
<td>96</td>
</tr>
<tr>
<td>0.76–1.49 mm</td>
<td>87</td>
</tr>
<tr>
<td>1.50–2.49 mm</td>
<td>75</td>
</tr>
<tr>
<td>2.50–3.99 mm</td>
<td>66</td>
</tr>
<tr>
<td>&gt;4.00 mm</td>
<td>47</td>
</tr>
</tbody>
</table>

**Choice of Corticosteroid Vehicle**

<table>
<thead>
<tr>
<th>Vehicle</th>
<th>Target skin site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creams</td>
<td>G, H, I</td>
</tr>
<tr>
<td>Foams</td>
<td>H, I</td>
</tr>
<tr>
<td>Gels</td>
<td>H</td>
</tr>
<tr>
<td>Lotions</td>
<td>H, I</td>
</tr>
<tr>
<td>Ointments</td>
<td>G, SH</td>
</tr>
</tbody>
</table>

\(G=\text{glabrous}, \ I=\text{intertriginous}, \ H=\text{hair bearing}, \ SH=\text{areas with sparse hair}\)

**Incidence of Dermatologic Side Effects with Prolonged Use of Topical Glucocorticoids**

<table>
<thead>
<tr>
<th>Drug Reaction</th>
<th>Incidence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telangiectasia</td>
<td>0.43%</td>
</tr>
<tr>
<td>Epidermal atrophy</td>
<td>0.15%</td>
</tr>
<tr>
<td>Hypertrichosis</td>
<td>0.08%</td>
</tr>
<tr>
<td>Striae</td>
<td>0.08%</td>
</tr>
<tr>
<td>Milia</td>
<td>0.07%</td>
</tr>
<tr>
<td>Acne</td>
<td>0.06%</td>
</tr>
<tr>
<td>Purpura</td>
<td>0.03%</td>
</tr>
<tr>
<td>Subcutaneous atrophy</td>
<td>0.03%</td>
</tr>
</tbody>
</table>

Psoriasis: see the section below

Proprietary agents: generic agents should not be assumed to have the same potency as brand name drugs. Subtle differences in the vehicle may affect potency.15

Dosing concentration: there is not a clear concentration–response effect.16

Dosing frequency: for class I agents there is no benefit of bid over qd dosing. For class II–V there is minimal or no difference between qd and bid dosing.17

Duration of treatment: if patients require more than six weeks of therapy for a persistent dermatologic problem, they should be referred to a dermatologist.

Anatomic site and side effects: there is an increase in telangiectasias, atrophy, and striae when potent agents are used on the face or in intertriginous areas.

Mometasone furoate and prednicarbate cause much less atrophy than other agents in the same class.

Table 13.3 Topical corticosteroids.

<table>
<thead>
<tr>
<th>Class/drug</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class I</strong></td>
<td></td>
</tr>
<tr>
<td>Clobetasol propionate ointment, cream (Temovate)</td>
<td>0.05</td>
</tr>
<tr>
<td>Betamethasone dipropionate ointment (Diprolene)</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Class II</strong></td>
<td></td>
</tr>
<tr>
<td>Fluocinonide gel, cream, ointment (Lidex)</td>
<td>0.05</td>
</tr>
<tr>
<td>Betamethasone dipropionate ointment, cream (Diprolene AF)</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Class III</strong></td>
<td></td>
</tr>
<tr>
<td>Triamcinolone acetate ointment (Aristocort A)</td>
<td>0.1</td>
</tr>
<tr>
<td>Mometasone furoate ointment (Elocon)</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>Class IV</strong></td>
<td></td>
</tr>
<tr>
<td>Fluocinolone acetonide ointment (Synalar)</td>
<td>0.025</td>
</tr>
<tr>
<td>Mometasone furoate cream (Elocon)</td>
<td>0.1</td>
</tr>
<tr>
<td>Triamcinolone acetonide ointment (Kenalog)</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>Class V</strong></td>
<td></td>
</tr>
<tr>
<td>Fluocinolone acetonide cream (Synalar)</td>
<td>0.025</td>
</tr>
<tr>
<td>Betamethasone valerate cream (Valisone)</td>
<td>0.1</td>
</tr>
<tr>
<td>Triamcinolone acetonide lotion (Kenalog)</td>
<td>0.1</td>
</tr>
<tr>
<td>Prednicarbate lotion (Dermatop)</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>Class VI</strong></td>
<td></td>
</tr>
<tr>
<td>Triamcinolone acetate cream (Aristocort)</td>
<td>0.1</td>
</tr>
<tr>
<td>Betamethasone valerate cream (Valisone)</td>
<td>0.05</td>
</tr>
<tr>
<td>Fluocinolone acetonide cream (Synalar)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Class VII</strong></td>
<td></td>
</tr>
<tr>
<td>Hydrocortisone cream</td>
<td>1, 2.5</td>
</tr>
<tr>
<td>Hydrocortisone acetate ointment</td>
<td>1</td>
</tr>
</tbody>
</table>

15 Olsen EA. A double blind controlled comparison of generic and trade-name topical steroids using the vasoconstriction assay. Arch Dermatol 1991;127: 197–201. Comparison of generic v proprietary preparations with the same active ingredients. Approximately 40% of the generic agents tested were ≥10% less potent than their proprietary counterparts.

16 Stoughton RB, Wullich K. The same glucocorticoid in brand name products. Does increasing concentration result in greater topical biological activity? Arch Dermatol 1989;125:1309–11. Randomized blinded trial in which Continued
Psoriasis†

Epidemiology
- Affects ~2% of the US population.
- Prevalence increases with age.
- Prevalence is greater in northern, colder climates.
- Family history plays a role in many patients.

Presentation
- Psoriasis is a chronic disease characterized by exacerbations and remissions.
- The primary lesion is a well demarcated erythematous plaque with adherent silvery scale.
- The lesions are usually symmetrical in distribution. Plaques may appear at sites of cutaneous trauma.

Categories
- Plaque-like: red, thick lesions with silvery scale and sharp borders. This is the most common form of psoriasis. It frequently affects the extensor surface of the extremities, but can appear anywhere.
- Guttate: numerous small tear drop shaped lesions, pink to salmon colored, with fine scaling. Usually located on the trunk, with sparing of the palms and soles. It may follow an episode of streptococcal upper respiratory infection. It can present as diffuse disease, with high fever and leukocytosis.
- Pustular: characterized by erythematous papules or plaques studded with pustules. Usually occurs on the trunk with sparing of the palms and soles. It can be localized or generalized.
- Erythrodermic: intense erythema covering most of the body without typical plaques. Malaise and fever are often present.

Treatment

Patient education helps patients cope with this chronic, occasionally disfiguring disease. The patient should understand the non-contagous nature of psoriasis, its chronic course, and the exacerbating factors: emotional stress, infection, trauma, xerosis, and certain medications (for example, systemic glucocorticoids, lithium, β blockers).

Localized disease (affecting <20% of body surface area)
- Topical corticosteroids: are the most commonly prescribed treatment. Their use is limited by side effects and tachyphylaxis. They should be used in combination with other agents, except for patients with mild or new disease.
- Calcipotriene (calcipotriol):18,19
  - Effects may not occur for 6–8 weeks.
  - Maximal benefit when used with topical corticosteroids.
  - Patients do not tachyphylax to this agent.
  - The possibility of hypercalcemia from use of this vitamin D analogue warrants caution in patients with a history of kidney stones.

One concentration of an agent was compared to a different concentration of the same agent in a vasoconstrictor assay on healthy subjects. For all five agents studied, there was either no change or an incomplete change in results with increasing drug concentration.

<table>
<thead>
<tr>
<th>Anatomic site</th>
<th>Class of agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elbows/ knees</td>
<td>I–III</td>
</tr>
<tr>
<td>extensor surfaces</td>
<td></td>
</tr>
<tr>
<td>Palms/soles</td>
<td>I, I*</td>
</tr>
<tr>
<td>Trunk</td>
<td>I–III</td>
</tr>
<tr>
<td>Scalp, mild</td>
<td>IV</td>
</tr>
<tr>
<td>Scalp with thick plaque</td>
<td>I–III with tar or salicylic acid</td>
</tr>
<tr>
<td>Genitalia</td>
<td>VI–VII</td>
</tr>
<tr>
<td>Intertiginous areas</td>
<td>VI–VII</td>
</tr>
</tbody>
</table>

* Treatment under occlusion with plastic wrap or hydrocolloid dressing.

Patients may contact the National Psoriasis Foundation for further information (http://www.psoriasis.org).


18 Kragbelle K, Gjertsen BT, De Hoop D et al. Double blind, right/left comparison of calcipotriol and betamethasone valerate in treatment of psoriasis vulgaris. Lancet 1991;337:193–6. The largest RCT of calcipotriene v a high potency steroid, it included 345 inpatients and outpatients. After six weeks, the disease severity score was reduced by 68.8% with calcipotriene and 61.4% with betamethasone valerate (P < 0.001).

19 Ashcroft DM, Po ALW, Williams HC, Griffiths CEM. Systematic review of comparative efficacy and tolerability of calcipotriol in treating chronic plaque psoriasis. BMJ 2000;320:963–7. Calcipotriene is superior to coal tar and short contact dithranol for mild to moderate chronic plaque psoriasis. In this study it had comparable efficacy with potent corticosteroids.
—Skin irritation occurs in ~20% of patients.
—Use with caution on the face and intertriginous areas.

- **Salicylic acid:** softens scaly plaques. It is used in conjunction with other agents.
- **Coal tar:** is most effective when used with other agents. It is malodorous and stains fabrics. It may cause folliculitis.
- **Tazarotene:** has modest efficacy in mild to moderate psoriasis. Usually used in combination with corticosteroids because of slow onset of action. It may cause local irritation and photosensitivity. Pregnancy category X.

**Generalized or resistant disease**

- Patients should be referred to a dermatologist for other appropriate therapy: ultraviolet B spectrum light (UVB), oral or topical psoralens plus ultraviolet A spectrum light (PUVA), methotrexate, or intralesional corticosteroids.

**Eczema**†,††,20,21

*Dermatitis* and *eczema* are vague terms that refer to inflammatory diseases of the skin. These disorders may present in any of the following stages and evolve or regress to another.

**Acute**

- Characterized by intensely pruritic, erythematous papules and vesicles overlying erythematous skin. Blisters may develop in a confluent or linear pattern.
- If secondary to contact dermatitis (for example, poison ivy), symptoms can begin hours to days after exposure.
- Treatment consists of cool wet dressings changed frequently, oral corticosteroids for intense or diffuse inflammation, antihistamines for itching, and oral antibiotics if there are signs of secondary bacterial infection.

**Subacute**

- Characterized by the presence of erythema and scaling, usually with indistinct borders. The presence of itching is variable. There may be cracking, fissuring, and a parched appearance.
- Treatment consists of class III–V topical corticosteroids, frequent application of emollients to dry skin, antihistamines, systemic antibiotics for staphylococcal superinfection, and coal tar agents for dermatitis that does not resolve.

**Chronic**

- Characterized by skin thickening, accentuation of skin lines (lichenification), fibrotic papules (prurigo nodularis) excoriation, and fissuring. Itching may be moderate to intense. Repetitive scratching can cause subacute disease to become chronic.
- Treatment is with class I–V corticosteroids. Intraleional steroid injection is an alternative for resistant lesions. Emollients may be helpful.

*Anthralin* is another topical agent for treatment of psoriasis. It is considered second line therapy because of its irritating and staining properties. It may be useful for chronic plaques.

21 There is no agreement and there are no guidelines concerning the use of the terms “eczema” or “dermatitis”. A review of five major textbooks of dermatology found that none of the taxonomies presented agreed with one another. Altekrueger I, Ackerman AB. Am J Dermatopathol 1994;16:517–22. The taxonomy presented in this chapter has been chosen for its simplicity.

**The etymology of “Eczema”**

“Eczema” derives from the Greek *ekzein*, which means “to boil out” or “to effervesce”. The term was introduced by Aetius of Amida when referring to pustular lesions, i.e. lesions that had a “boiling out of pus”. Altekrueger I, Ackerman AB. Am J Dermatopathol 1994;16:517–22.

**Types of eczema/dermatitis and their category of presentation**

<table>
<thead>
<tr>
<th>Type of Eczema/dermatitis</th>
<th>Acute</th>
<th>Subacute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asteatotic eczema</td>
<td>S</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>S</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Contact allergy</td>
<td>A, S</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatophyte infection</td>
<td>A, S</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyshidrosis</td>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fingertip eczema</td>
<td>S, C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intertrigo</td>
<td>S</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lichen simplex chronicus</td>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nummular eczema</td>
<td>S, C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A = acute, S = subacute, C = chronic</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Atopic dermatitis
- Skin testing or in vitro IgE testing may be useful in assessment of food or airborne allergy as a cause of dermatitis. These tests have a high negative predictive value for ruling out suspected allergens. Positive tests, however, do not prove that an allergen is causing clinical symptoms. Controlled food challenges or elimination diets may help to confirm causation. Avoidance of food or airborne allergens is the recommended goal.22
- There is some evidence that control of house dust mite antigens reduces symptoms in patients with a positive RAST test, but only if very low levels of dust mite antigens are achieved. Use of polyurethane coated mattress, pillow, and duvet covers or washing bedding at 55°C (131°F) are the most effective means of achieving low antigen levels.23
- Adjustment of diet to avoid suspected allergens is logical, but is not yet proven.23

Contact dermatitis (allergic and irritant types)
- Induced by physical contact with an allergen or an irritating, non-allergenic substance (for example, soap, organic solvents).
- The intensity of irritant dermatitis varies with the concentration of the offending agent, duration of exposure, and the patient’s susceptibility. Hand washing dermatitis is a common example.
- Contact allergens may have typical distribution patterns. For example, an allergy to the nickel in a bracelet may cause a rash around the wrist.
- The history should include the date of onset; the relationship of symptoms to workday, weekend, and vacation; and cosmetics, lotions, or topical medications.
- If avoidance of the suspected agent does not result in resolution of symptoms, referral to an allergist for allergen patch testing is appropriate.

Dermatophyte infections†
These infections are most commonly caused by Microsporum, Trichophyton, and Epidermophyton species. They can be transmitted by fingers, fomites, animals, and, uncommonly, through soil. There is a higher incidence in immunosuppressed patients.

Tinea pedis (athlete’s foot)
- It is usually localized to the third and fourth interdigital spaces as well as the sole.
- Vesicles are usually present if there is an acute phase. Maceration and scaling occur later.
- Occlusive footwear and hot, humid weather are predisposing factors.
Tinea unguium (onychomycosis)
- Fungal infection of the nails affects 15–20% of adults aged 40–60. Diagnosis should be established with a KOH prep and a culture, as 50% of thick nails do not have infection.
- Topical agents are effective for dermatophyte infections of the skin, but are of little benefit in nail infections.
- Wash and fully dry skin prior to application of agent.

Benefit of Topical Antifungal Agents for Skin Infections

<table>
<thead>
<tr>
<th>Comparison</th>
<th>RR of treatment failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciclopiroxolamine v placebo</td>
<td>0.14</td>
</tr>
<tr>
<td>Undecenoic acid v placebo</td>
<td>0.28</td>
</tr>
<tr>
<td>Allylamines v placebo</td>
<td>0.30</td>
</tr>
<tr>
<td>Tolnaftate v placebo</td>
<td>0.46</td>
</tr>
<tr>
<td>Azoles v placebo</td>
<td>0.54</td>
</tr>
<tr>
<td>Allylamines v azoles</td>
<td>0.88</td>
</tr>
</tbody>
</table>

- Consider oral antifungals for resistant skin infections.
- For toenail infections, terbinafine is the treatment of choice.25,26

Continuous Terbinafine v Intermittent Itraconazole for Onychomycosis

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Rate of clinical cure (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous terbinafine</td>
<td></td>
</tr>
<tr>
<td>12 week course</td>
<td>54</td>
</tr>
<tr>
<td>16 week course</td>
<td>60</td>
</tr>
<tr>
<td>Intermittent itraconazole</td>
<td></td>
</tr>
<tr>
<td>12 week course</td>
<td>32</td>
</tr>
<tr>
<td>16 week course</td>
<td>32</td>
</tr>
</tbody>
</table>

Seborrheic dermatitis

Presentation
- More common in patients with AIDS and central nervous system disorders, but does occur in otherwise healthy patients.
- Characterized by mild to moderate erythema with fine to medium scaling. The borders are not well defined like those of psoriasis plaques.
- Affects areas of the skin with high concentrations of sebaceous glands: the scalp, eyebrows, eyelashes, moustache, beard, and the nasolabial folds. It may also appear on the trunk.
- It is typically symmetric, affecting both sides of the body.
- The patient may present complaining of dandruff.

Treatment27
- **Face:** frequent washing with selenium sulfide or zinc shampoo. Topical azole and/or hydrocortisone cream once or twice daily.
- **Scalp and beard**: selenium sulfide or zinc shampoo. If the scalp is covered with thick scale, apply olive oil for several hours and then wash with a tar shampoo. Alternatively, apply a coal tar–salicylate mixture overnight.

### Table 13.4 Sunscreens, with ranges of ultraviolet light protection.

<table>
<thead>
<tr>
<th>Active ingredients</th>
<th>Abbreviation</th>
<th>Partial UVB</th>
<th>Full UVB</th>
<th>Partial UVA</th>
<th>Full UVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Para-aminobenzoic acid and its esters</td>
<td>P</td>
<td>✓</td>
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<td>Cinnamates</td>
<td>C</td>
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<td>Salicylates</td>
<td>S</td>
<td>✓</td>
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<tr>
<td>Benzophenones</td>
<td>B</td>
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<td>✓</td>
<td>✓</td>
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<tr>
<td>Octocrylene</td>
<td>O</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
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<tr>
<td>Titanium dioxide</td>
<td>T</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Zinc oxide</td>
<td>Z</td>
<td>✓</td>
<td></td>
<td>✓</td>
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</tr>
</tbody>
</table>

**Sunscreen brand**

<table>
<thead>
<tr>
<th>Active Ingredients</th>
<th>SPF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bain de Soleil All day waterproof sunblock</td>
<td>C, B, O, T</td>
</tr>
<tr>
<td>Coppertone All day waterproof sunblock lotion</td>
<td>C, B</td>
</tr>
<tr>
<td></td>
<td>C, S, B</td>
</tr>
<tr>
<td>Coppertone Moisturizing sunblock lotion</td>
<td>C, B</td>
</tr>
<tr>
<td>Neutrogena Sunblock lotion</td>
<td>C, B</td>
</tr>
<tr>
<td></td>
<td>C, S, B</td>
</tr>
<tr>
<td>Neutrogena Sensitive skin sunblock</td>
<td>T</td>
</tr>
</tbody>
</table>
14 Diabetes mellitus
Louis J Capponi

Epidemiology
Prevalence
- One million Americans have type 1 diabetes, formerly known as insulin dependent diabetes mellitus (IDDM).
- Fifteen million Americans have type 2 diabetes, formerly known as non-insulin dependent diabetes mellitus (NIDDM). It is estimated that a third of these cases are undiagnosed.
- Patients with type 1 diabetes usually present in childhood and adolescence, while type 2 patients usually present after the age of 45. However, with the increased prevalence of obesity, many people in their 20s and 30s are now presenting with type 2 diabetes.
- Risk factors include obesity, a first degree relative with diabetes, glucose intolerance, and gestational diabetes.

Morbidity and mortality
- In 1998, diabetes was the seventh leading cause of death in the US, causing 64,751 deaths.
- Heart disease and stroke are 2–4 times more common in diabetic patients.
- Coronary artery disease is present in 75% of diabetes related deaths. There are more than 77,000 deaths due to heart disease in diabetic patients per year.
- Diabetes contributes to 56,000 amputations per year.
- Diabetes is the leading cause of new cases of blindness in people aged 20–74.
- Diabetes is the leading cause of endstage renal disease – 40% of cases are related to diabetes.
- Peripheral neuropathy occurs in 50% of diabetic patients at 15 years.

Diagnosis
Laboratory criteria for the diagnosis of diabetes
Any one of the following:
- a glucose value of $\geq 126$ mg/dl after an eight hour fast
- a random glucose $\geq 200$ mg/dl and symptoms of diabetes
- a glucose $\geq 200$ mg/dl two hours after a 75 gram glucose load.

An abnormal test must be confirmed by repeat testing (of the same or one of the other two criteria) on a subsequent date.
- Impaired fasting glucose: fasting glucose 110–125 mg/dl.
- Impaired glucose tolerance: glucose 140–199 mg/dl two hours after a 75 gram oral glucose load.

Conflicting screening recommendations
- The 1997 ADA Expert Committee Report recommended considering screening patients for diabetes with a fasting glucose level every three years beginning at age 45 (younger if risk factors are present).

Guideline recommendations in this chapter have been adapted from:


Glucose conversion formula:
18 mg/dl = 1 mM/l

4 Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997;20:1183–97. The report explains the rationale for the new diagnostic criteria. The threshold for diagnosis was lowered from a fasting glucose of $\geq 140$ to $\geq 126$ mg/dl.

5 The extent to which impaired glucose tolerance predicts who will develop diabetes has been broadly debated. One summary of studies reports a 15–45% incidence at 10 year follow up. Yudkin JS, Alberti KG, McLarty DG, Suss AB. Impaired glucose tolerance. BMJ 1990; 301:397–402. The oral glucose tolerance test is not recommended for routine clinical use.
• The 1996 US Preventive Services Task Force⁶ gave diabetes screening a “C” recommendation (not enough evidence to recommend for or against).

**History**
- Polyuria
- Thirst
- Weight loss
- Blurry vision

**Physical exam**
- Weight (target BMI: < 25 kg/m²)
- Blood pressure (target: 130/85)
- Retina exam
- Foot exam (for skin breakdown, inability to feel a 10g monofilament applied to the dorsum, decreased pulses)

**Labs**
- Glycated hemoglobin (also known as glycohemoglobin, glycosylated hemoglobin, and HbA₁c) measures overall glucose levels during the previous 2–3 month period.
- Glucose (normal: < 110 mg/dl)
- Potassium, BUN/creatinine
- Fasting lipid profile – both ADA and the National Cholesterol Education Program Adult Treatment Program (2001) guidelines recommend an LDL target of < 100 mg/dl for all diabetic patients.
- Urinalysis for protein: – 24 hour collection or morning spot urine albumin/creatinine ratio (UACR).⁷ An albumin/creatinine ratio >30 mg/g indicates microalbuminuria. Diabetic patients with microalbuminuria should be treated with an ACE inhibitor, even if normotensive.

**Treatment**

**Overview**

*Major objectives of treatment*
- Prevention of symptoms: polyuria, polydipsia, weight loss, polyphagia, blurry vision, dehydration.
- Prevention of complications:
  - Macrovascular: myocardial infarction, stroke, sudden cardiac death, peripheral vascular disease
  - Microvascular: nephropathy, retinopathy, neuropathy

*Strategy for prevention of complications*
- Calorie restriction and weight loss⁸
- Control of hyperglycemia with oral medications and insulin
- Aggressive control of blood pressure and albuminuria with an ACE inhibitor
- Cholesterol lowering
- Smoking cessation

---


The National Glycohemoglobin Standardization Program began in 1996 to reconcile the various assays used. Glycated hemoglobin and HbA₁c are not the same thing and the terms should not be used interchangeably. It is essential to know the upper limit of normal of the assay being used.


Urine dipsticks are not sensitive enough to detect microalbuminuria (30–300mg/24 hours), the earliest stage of diabetic nephropathy.

⁸ The goal is a BMI of < 25 kg/m² (see the BMI table in Chapter 30). Past recommendations for a high carbohydrate/low fat diet have been questioned. Garg A, Bantle JP, Henry RR et al. Effects of varying carbohydrate content of diet in patients with non-insulin dependent diabetes mellitus. JAMA 1994;271:1421–8. See further discussion in section on diet.
Patient education

- Perhaps more than any other major disease, diabetes requires active participation by the patient for effective treatment. Education should be a major focus at every office visit.
- Diabetic diet
- Medications and insulin injections
- Home glucose monitoring
- Foot care
- Compliance with screening

Diet

Weight loss

- A number of trials have shown that hypocaloric diets substantially reduce blood glucose. However...
- Much of the improvement in glucose control is probably due to the temporary decrease in caloric intake that takes place during the dieting period rather than the weight loss itself.9
- Weight loss is very difficult to achieve, let alone maintain. Most patients who are advised to lose weight do not experience long term success.10

Meal spacing

- Type 2 diabetic patients who are unable to respond to large carbohydrate loads may be able to mount an adequate insulin response to well spaced smaller meals. Meal spacing may also help to prevent episodes of hypoglycemia.
- In fact, multiple studies have shown that spreading intake throughout the day with small meals and snacks does dampen blood glucose extremes but has only modest effects on average glucose levels.11
- Theoretical drawbacks to frequent smaller feedings include the potential for weight gain and difficulty with compliance.

Carbohydrate intake

- Traditional teaching in diabetic diets has favored starches over sweets. A considerable body of evidence has essentially contradicted this maxim and there are currently no clear answers as to the appropriate composition of carbohydrates in a diabetic diet.
- The glycemic index (GI) is a standardized measure of blood glucose response to the ingestion of a given substance. Lists of the GI for most common foods have been reported in the literature and yield a number of surprises. For example, using white bread as a standard of 100, an equivalent carbohydrate content of honey yields a GI of 126, of sucrose 86, of bananas 79, of frozen peas 74, and of ice cream 52.12
- Using tools such as the GI, investigators are beginning to explore non-traditional diabetic diets as a way to improve glucose control.13

9 Wing RR, Blair EH, Bononi P et al. Caloric restriction per se is a significant factor in improvements in glycemic control and insulin sensitivity during weight loss in obese NIDDM patients. Diabetes Care 1994;17:30–6. When 30 diabetic subjects were fed a very low calorie diet of 330 calories per day, the average glucose level decreased from 297 to 158mg/dl.2 When subjects resumed isocaloric feedings, about half of the original glucose gain disappeared even though the original weight loss was preserved.
13 Gannon MC, Nuttall FQ, Westphal SA, Fang S, Excan-Fang N. Acute metabolic response to high-carbohydrate, high starch meals compared with moderate-carbohydrate, low-starch meals in subjects with type 2 diabetes. Diabetes Care 1998;21:1619–26. When a traditional (high carbohydrate) diabetic diet was compared to an isocaloric experimental diet that emphasized sucrose and fructose rich carbohydrates rather than usual starches such as bread and potatoes,
Fat intake
- The risk of coronary artery disease has led the ADA in the past to recommend strict controls in dietary fat intake and to emphasize carbohydrates as the chief energy source. Nonetheless, substitution of carbohydrates with monounsaturated fats has been gaining acceptance.
- For example, compared to a traditional high carbohydrate diet, a high monounsaturated fat diet (50% fat) decreased blood glucose by 14%, serum triglycerides by 25%, and insulin doses by 14% without affecting LDL cholesterol or weight in type 2 diabetic patients on insulin therapy.\(^{14}\)

Protein intake
- Despite some evidence suggesting that a very low protein diet may modestly slow progression of renal disease in non-diabetic patients,\(^{15}\) there are no simply no reliable data to guide the management of diabetic patients without overt nephropathy.
- For dietary protein intake, the ADA states simply that there is insufficient evidence to recommend any particular intake level and suggests that diabetic patients adhere to the adult Recommended Dietary Allowance (RDA) of 0.8 grams per kilogram per day.\(^{16}\)

Summary of dietary principles
- Weight loss is an effective strategy for glucose control in the few patients who are able to achieve it.
- Spreading out the caloric intake dampens the highs and lows of serum glucose but has little effect on average glucose levels.
- The chief dietary contributors to hyperglycemia are carbohydrates of all types. Complex carbohydrates do not appear to be less hyperglycemic than simple sugars.
- Regardless of total fat intake, diabetic diets should emphasize monounsaturated fats over other dietary sources of fat.
- The appropriate intake of protein in a diabetic diet is not currently known.

Drug therapy

Effectiveness

Type 1 diabetes: the DCCT
- The Diabetes Control and Complications Trial (DCCT)\(^{17}\) was the landmark trial that showed that intensive control of glucose (with 3–4 injections per day or an insulin pump) in type 1 diabetic patients reduced the progression of all three micro-vascular complications as compared with conventional therapy (1–2 injections per day).
- 1141 type 1 diabetic patients aged 13–39, of which 726 were free of retinopathy (primary prevention) and 715 already had retinopathy (secondary prevention), were randomized to conventional or intensive therapy and followed for 6.5 years. Event rates (rate per 100 patient years) were as follows.


Mode of Prevention

<table>
<thead>
<tr>
<th></th>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Conven-</td>
<td>Intensive</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>4.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Micro-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>albuminuria</td>
<td>3.4</td>
<td>2.2</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>9.8</td>
<td>3.1</td>
</tr>
</tbody>
</table>

- Significant hypoglycemic events were three times higher in the intensive therapy group (62 v 19 per 100 patient years).
- There was no difference in episodes of DKA.
- Patients on intensive therapy gained an average of 4.6 kg more than those in the conventional group.
- The benefits of intensive therapy persisted four years after the trial was completed, despite gradually increasing serum glucose.18

**Intensive treatment of type 2 diabetes: the UKPDS**

- The United Kingdom Prospective Diabetes Study19 (UKPDS) was a complex trial with several arms and multiple drug crossover protocols. The basic design was a 10 year prospective analysis of 3867 newly diagnosed type 2 diabetic patients (mean age 54) randomized to conventional dietary therapy or intensive therapy with insulin or sulfonylureas. Obese patients could receive metformin.
- The intensive therapy group achieved a modestly lower HbA1c (7.0% v 7.9%) and an overall 25% reduction in the frequency of microvascular complications. For every 20 patients treated for 10 years with intensive therapy, one microvascular endpoint (retinal photocoagulation, most commonly) was prevented.
- There was no difference in macrovascular complications or all-cause mortality.
- More patients in the intensive therapy group experienced severe hypoglycemia (1.0–1.8% v 0.7%). On average, they gained 2.9 kg more than those in the conventional diet group.
- Importantly, the benefits of lowering glucose were seen at all glycemic levels; there was no threshold for benefit. This helped confirm the role of direct glucose toxicity in diabetic complications. For every point decrease in HbA1c, there was a 35% reduction in the risk of complications.
- The UKPDS also confirmed that type 2 diabetes is a progressive disorder. Glucose levels rose consistently over time in all groups, as was seen in the DCCT trial of type 1 diabetes.
- This study helped refute the idea that sulfonylureas might increase cardiovascular mortality, as suggested by an older study.20

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20 University Group Diabetes Program. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. Diabetes 1976;25:1129–33. This study suggested that there was an increase in cardiovascular mortality with the first generation sulfonylurea tolbutamide.
Hypoglycemia

- Optimal management of diabetes entails achieving the best glucose control possible without causing hypoglycemia (glucose < 70 mg/dl).
- Severe hypoglycemia can cause seizures, loss of consciousness, coma, and death.
- Treatment should be tailored to the patient’s ability to understand, detect, and treat hypoglycemic episodes when they occur. Patients taking hypoglycemic medications (sulfonylureas, repaglinide, insulin) should always have a source of carbohydrates readily available.
- For hypoglycemic emergencies, glucagon 1 mg SQ, IM, or IV may be given. Family members may be taught how to administer glucagon.

Hypoglycemic agents

- Until 1995, sulfonylureas and insulin were the only drugs available in the US to treat type 2 diabetes. Since then, three additional classes of drugs have been approved by the FDA: biguanides, α-glucosidase inhibitors, and thiazolidinediones.

Sulfonylureas

- The second generation sulfonylureas glyburide (Diabeta, Micronase), glipizide (Glucotrol), and glimepiride (Amaryl) are the most widely used oral agents and exhibit similar efficacy.
- The sulfonylureas work primarily by increasing insulin production by the pancreas; they therefore share some of the undesirable side effects of insulin: hypoglycemia, hyperinsulinemia, and weight gain.
- Sulfonylureas lower glycosylated hemoglobin by 1.5–2.0 percentage points. About one quarter of all patients started on sulfonylurea monotherapy will achieve adequate glucose control. The rest will require a second agent.
- Sulfonylureas can cause hypoglycemia and should be used with caution in elderly people.
- Repaglinide (Prandin) is technically a meglitinide, but has the same mechanism of action as sulfonylureas.
- Repaglinide is less potent than the sulfonylureas, but its rapid onset and short half-life make it helpful in lowering postprandial hyperglycemia if taken before meals.

Biguanides

- Metformin (Glucophage) decreases hepatic glucose production (both gluconeogenesis and glycogenolysis), improves insulin resistance by promoting glucose uptake in peripheral tissue and may delay intestinal glucose absorption.
- Unlike the sulfonylureas and insulin, metformin does not produce hypoglycemia, hyperinsulinemia, or weight gain. It is associated with decreased LDL cholesterol and triglycerides.
- Initially, metformin can lower glycosylated hemoglobin by 1–2 percentage points.


21 These numbers represent the initial effect of therapy. Clinical trials of oral diabetes medications are almost always of short duration. UKPDS clearly demonstrated the progressive nature of diabetes.
In UKPDS 34, a subgroup of 1704 overweight patients was randomized to receive metformin, insulin, sulfonylureas, or conventional diet therapy. Event rates at 10 years are as follows.

<table>
<thead>
<tr>
<th></th>
<th>Metformin</th>
<th>Insulin or sulfonylureas</th>
<th>Diet (v diet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes endpoints</td>
<td>29%</td>
<td>37%</td>
<td>39%</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>15%</td>
<td>20%</td>
<td>22%</td>
</tr>
</tbody>
</table>

NNT: number needed to treat for 10 years to prevent one event

- These remarkable benefits were seen despite only modest improvements in glucose control: HbA1c was 7.4% in the metformin group compared with 8.0% in the conventional diet group.
- In UKPDS 34, a subgroup of 537 patients who had poor glucose control despite sulfonylurea therapy for seven years were randomized to additional therapy with metformin (N = 268) or placebo (N = 269). After four years, there was a 96% increase in diabetes related death in the sulfonylurea-metformin group versus the sulfonylurea monotherapy group. The absolute numbers of MIs (33 and 31) and strokes (15 and 13) were similar, but more patients in the combination group had fatal MIs and fatal strokes. This result has led to considerable controversy (see reference 23).
- Metformin plus sulfonylurea has shown benefit in short term trials with surrogate endpoints.
- Lactic acidosis is a rare complication of metformin but has a high mortality rate. Most cases occur in patients with renal insufficiency.
- Metformin is contraindicated in patients with renal insufficiency (creatinine > 1.5 for males, > 1.4 for females), hepatic insufficiency, history of acidosis, or alcohol abuse.
- Metformin should be avoided in patients with conditions that predispose them to low flow states such as significant congestive heart failure or peripheral vascular disease. It should be discontinued several days before surgery or any procedure requiring radiocontrast dye.
- The main side effect is GI upset. Many patients experience diarrhea initially, but this usually resolves with continued use.

Thiazolidinediones
- Pioglitazone (Actos) and rosiglitazone (Avandia) decrease insulin resistance in peripheral tissues, particularly skeletal muscle and adipose tissue. They also decrease hepatic gluconeogenesis.
- Like metformin, they do not cause hypoglycemia, weight gain, or hyperinsulinemia. However, caution must be exercised when troglitazone is combined with agents that do cause hypoglycemia.

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23 UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998; 352:854–65. The argument has been made that the numbers were too small, and the follow up of four years too short, to make any extrapolation. Other commentators have suggested that the mortality rate in the sulfonylurea group was lower than expected. The ADA still recommends use of these agents in combination and it is a common clinical practice. This result continues to be debated.

24 DeFronzo RA, Goodman AM. The Multicenter Metformin Study Group. Efficacy of metformin in patients with NIDDM. N Engl J Med 1995;333:541–9. In a six month study, metformin and glyburide monotherapies were equally efficacious. Combination therapy was superior to either drug alone and exhibited improved lipid profiles.

25 Wilhelm BE, Myrbed M. Metformin-associated lactic acidosis in Sweden 1977–1991. Eur J Clin Pharmacol 1993;44:389-91. Three cases of lactic acidosis were reported per 100 000 patient years. No cases were reported in the UKPDS study.
Troglitazone (Rezulin) was withdrawn from the US market in 2000 by the FDA because of 90 cases of liver failure leading to 63 deaths and 10 transplants among the 1.9 million people who took the drug (~1 in 20,000).

While the same number of adverse events have not been reported with the other thiazolidinediones, liver function tests are recommended every two months for the first year of therapy and periodically thereafter.

Because of liver toxicity, thiazolidinediones are not recommended as first line therapy, but can be added as a second or third agent.\(^{26}\)

Thiazolidinediones may have beneficial effects on other cardiovascular risk factors such as blood pressure, lipids, fibrinolysis, and carotid artery intima media thickness, but much of this research is still preliminary.\(^{27}\)

**α-Glucosidase inhibitors**

- Acarbose (Precose) and miglitol (Glyset) delay the absorption of glucose, lowering postprandial glucose and insulin levels.
- α-Glucosidase inhibitors are less potent than the other oral agents, but can lower HbA\(_{1c}\) by 0.5–1.0 percentage points when added to metformin, a sulfonylurea, or insulin.\(^{28}\)
- These agents are most helpful for controlling postprandial hyperglycemia.
- They must be taken with the first bite of each meal so that they are present with food in the small bowel.
- Flatulence, bloating, diarrhea, and abdominal discomfort are the most troublesome side effects. These can be minimized by starting at extremely low doses (acarbose 25 mg qd or bid) and gradually increasing to the maximum dose of 100 mg tid.

**Insulin**

**General principles of insulin use**

- Insulin should be used in all type 1 diabetic patients and in type 2 diabetic patients where oral therapy has failed.\(^{29}\) It may be considered as first line therapy in type 2 diabetic patients with symptoms and/or glucose levels > 300 mg/dl. The progressive nature of the disease suggests that the majority of type 2 diabetic patients will eventually require insulin therapy alone or in conjunction with oral agents.
- Any regimen of insulin may be combined with oral agents in type 2 diabetic patients.
- The goal is to achieve glycemic control throughout 24 hours as documented by home monitoring.
- The chief danger is hypoglycemia. Dosing changes should be gradual and the patient should be educated about the signs, symptoms, and treatment of hypoglycemia. The other major side effect is weight gain. Both of these side effects occur more commonly with insulin than with sulfonylureas.\(^{30}\)
- Active patient education, participation, and self monitoring are vital to success with insulin. There are many ways to initiate insulin therapy.

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\(^{26}\) Fonseca V, Rosenstock J, Patwardhan R, Saleman A. Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus. JAMA 2000;283:1695–702. 348 diabetic patients failing oral therapy were randomized to metformin 2.5 g/day plus rosiglitazone or placebo for 26 weeks.

<table>
<thead>
<tr>
<th>Glyc Hb change</th>
<th>Rosiglitazone 4 mg/day</th>
<th>Rosiglitazone 8 mg/day</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>−0.56%</td>
<td>−0.78%</td>
<td>+0.45%</td>
</tr>
</tbody>
</table>


\(^{28}\) Chiasson JL, Josse RG, Hunt JA et al. The efficacy of acarbose in the treatment of patients with non-insulin-dependent diabetes mellitus. A multicenter controlled clinical trial. Ann Intern Med 1994;121:928–33. Acarbose or placebo was given to 354 patients who were already being treated with diet alone, sulfonylurea, or insulin. At one year postprandial glucose decreased from 342 to 279 mg/dl (mean of all groups). HbA\(_{1c}\) decreased by 0.4–0.9 percentage points.

\(^{29}\) Hayward RA, Manning WG, Kaplan SH, Wagner EH, Greenfield S. Starting insulin therapy in patients with type 2 diabetes: effectiveness, complications, and resource utilization. JAMA 1997;278:1663–9. This cohort study of 8668 patients attempted to evaluate the effectiveness of insulin therapy in actual clinical practice (HMO with general internists) as opposed to the highly monitored research setting of most studies. After a year of insulin therapy, average HbA\(_{1c}\) decreased by 0.9 percentage points. At two years, 60% of patients had HbA\(_{1c}\) levels >8%, testifying to the difficulty of treating this disease.

\(^{30}\) UKPDS 24. A six-year, randomized, controlled trial comparing sulfonylurea, insulin, and metformin therapy in patients with newly diagnosed type 2 diabetes that could not be controlled with diet therapy. Ann Intern Med 1998;128:165–73. Compared to patients on sulfonylureas, those on insulin...
Insulin dosing

- In type 2 diabetic patients, insulin is often initiated with bedtime NPH, alone or in conjunction with oral therapy. Typical starting doses are 10 units qHS, increasing by 5–10 units at a time to control AM fasting glucose (one injection per day).
- In type 1 diabetic patients, NPH/regular combinations may be given before breakfast and supper (two injections per day), using the “insulin formula”:

  \[ \text{60\% of the weight in kilograms = daily number of units} \]

  \[ \frac{2}{3} \text{ in the morning, } \frac{1}{3} \text{ in the evening} \]

  \[ \text{NPH/regular ratios = } \frac{2}{1} \text{ am, } \frac{1}{1} \text{ pm} \]

- If middle of the night hypoglycemia is a problem, the evening NPH dose can be delayed until bedtime (three injections per day).
- Very long acting insulin (Ultralente) may be combined with doses of regular insulin before each meal (three injections per day). It cannot be combined with NPH in the same syringe because of altered pharmacokinetics.
- Lispro is a synthetic insulin analog which has lysine and proline switched at positions 28 and 29 on the α-chain. Lispro does not form polymers as easily as regular insulin and is absorbed more rapidly. It may be useful for patients who cannot eat on a predictable schedule – hence the nickname “snack insulin”.
- Inhaled insulin is being investigated as an alternative to needle injections.31

Combination therapy

- Most patients will eventually require more than one drug to achieve glucose control.32
- Despite the lingering questions from UKPDS 34, most clinicians combine sulfonylurea with metformin.
- Thiazolidinediones are commonly added as second or third medications.33
- Adding an evening dose of insulin to two or three oral agents may be useful in patients with inadequate control or who are hesitant to switch completely to insulin.34
- Type 2 diabetic patients who are already on insulin may sometimes benefit from the addition of an oral agent, particularly metformin,35 in an attempt to lower the total insulin dose.

ADA Glycemic Targets

<table>
<thead>
<tr>
<th>Glycemic Target</th>
<th>Target</th>
<th>Intensify Therapy at</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preprandial glucose</td>
<td>80–120 mg/dl</td>
<td>&gt; 140 mg/dl</td>
</tr>
<tr>
<td>Bedtime glucose</td>
<td>100–140 mg/dl</td>
<td>&gt; 160 mg/dl</td>
</tr>
<tr>
<td>HbA1c(^*)</td>
<td>&lt; 7.0%</td>
<td>&gt; 8.0%</td>
</tr>
</tbody>
</table>

\(^*\)Non-diabetic reference range: 4.0–6.0%

Example: 198 lb (90 kg) male 54 units per day
am: 36 units \((24 \text{N}/12 \text{R})\) pm: 18 units \((9 \text{N}/9 \text{R})\)

34 Yki-Jarvinen H, Ryysy L, Nikkila K et al. Comparison of bedtime insulin regimens in patients with non-insulin-dependent diabetes mellitus: a randomized controlled trial. Ann Intern Med 1999;130:889–96. 96 patients failing sulfonylureas were followed for one year on bedtime NPH plus metformin, glyburide, both, or morning insulin. Patients in the NPH/metformin group had the biggest drop in HbA1c (−2.5 points), the least weight gain (+0.9 kg) and the fewest hypoglycemic episodes (1.8 per patient).
35 Avilés-Santa L, Sinding J, Raskin P. Effects of metformin in patients with poorly controlled, insulin-treated type 2 diabetes mellitus. Ann Intern Med 1999;131:182–8. 43 patients on insulin were given metformin or placebo. At 24 weeks:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Insulin use</th>
<th>HbA1c(^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>−4.5 U/d</td>
<td>−2.5</td>
</tr>
<tr>
<td>Placebo</td>
<td>+23 U/d</td>
<td>−1.6</td>
</tr>
</tbody>
</table>
Self monitored blood glucose (SMBG): counseling patients about fingersticks

- Patients should be encouraged to check fingersticks not only to avoid hypoglycemia and adjust insulin but also to understand the effect of diet and activity on their diabetes.
- Patients on insulin should measure blood glucose prior to administering their insulin and all patients should check whenever they suspect that they are hypo- or hyperglycemic.
- “Sliding scale” regular insulin can be added to the basic regimen when fingerstick results are too high.
- The ADA recommends SMBG for all diabetic patients.

Adjusting a twice-daily insulin regimen using the patient’s fingerstick log

- Assuming a regimen of NPH/regular before breakfast and dinner:

  Pre-breakfast fingerstick reflects... pre-dinner NPH
  Pre-lunch fingerstick pre-breakfast regular
  Pre-dinner fingerstick pre-breakfast NPH
  Bedtime fingerstick pre-dinner regular
  1–7 am fingerstick pre-dinner NPH

- Small adjustments to the regimen are safer than large ones.
- If the fingerstick is above target on three successive days, raise the dose of the related insulin by 10%.
- If a reading is below 70 mg/dl, reduce the related insulin dose by 15%.
- If hypoglycemia occurs in the middle of the night, consider giving NPH at bedtime rather than before dinner.
- The standard pre-breakfast/pre-dinner fingerstick schedule mainly provides information on the action of NPH insulin. In order to make informed changes in the dose of regular insulin, fingersticks before lunch and at bedtime are necessary. Patients should be encouraged to vary the time of their fingersticks and to record the times in their logs, explaining any abnormally high or low glucose levels.

Suggested health maintenance

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foot exam</td>
<td>Each visit</td>
</tr>
<tr>
<td>Glycosylated hemoglobin</td>
<td>Quarterly</td>
</tr>
<tr>
<td>UACR or 24 hour urine for protein</td>
<td>Yearly</td>
</tr>
<tr>
<td>Dilated retina exam</td>
<td>Yearly</td>
</tr>
<tr>
<td>Influenza vaccine</td>
<td>Yearly</td>
</tr>
<tr>
<td>Pneumococcal vaccine</td>
<td>Once</td>
</tr>
<tr>
<td>PPD36</td>
<td>Yearly unless positive</td>
</tr>
</tbody>
</table>

Prevention and treatment of complications

Foot care

- Examine the feet and shins every visit and review foot care frequently.

To begin a patient on SMBG...

- Glucometer
- Lancets
- Glucometer test strips
- Alcohol pads

SMBG: the proper sequence

1. Fingerstick
2. Insulin
3. Meal

The higher the fingerstick, the longer the patient should wait before eating.

“Sliding Scale” Regular Insulin

<table>
<thead>
<tr>
<th>Glucose (mg/dl)</th>
<th>Units of insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>150–200</td>
<td>1–3</td>
</tr>
<tr>
<td>200–250</td>
<td>2–6</td>
</tr>
<tr>
<td>250–300</td>
<td>3–9</td>
</tr>
<tr>
<td>300–350</td>
<td>4–12</td>
</tr>
<tr>
<td>350–400</td>
<td>5–15</td>
</tr>
</tbody>
</table>

Higher doses may be required in patients with insulin resistance.

36 PPD positive diabetic patients have a risk of developing tuberculosis 2–4 times that of patients without diabetes, particularly in poorly controlled type 1 patients. Vitamin B₆ should be added to INH because of increased risk for neuropathy in diabetic patients. Bass JB Jr, Farer LS, Hopewell PC et al. Treatment of tuberculosis and tuberculosis infection in adults and children. Am J Respir Crit Care Med 1994;149:1359–74.
• Check for peripheral pulses, ulcers, fungal infections, corns, calluses, early skin breakdown, and symptoms of neuropathy.
• Screen yearly for neuropathy using the monofilament test. Patients who are unable to sense the 10 gram load applied to four points on the dorsum of the foot should be counseled more thoroughly about foot care and referred to a podiatrist.
• Encourage patients to change shoes at mid-day.
• Infections should be treated aggressively. Typical signs of infection may be absent in patients with limb threatening disease.

Neuropathy
• The tricyclic antidepressants amitriptyline and desipramine have been shown to reduce symptomatic peripheral neuropathy by 60–74%. The lowest dose possible should be used, but patients may need the equivalent of 150 mg of amitriptyline or more.
• The more costly antiepileptic drug gabapentin is also effective for diabetic neuropathy, but in a randomized trial was not found to be superior to amitriptyline.
• Topical capsaicin cream 3–4 times per day is useful for pain.
• Diabetic gastroparesis can be treated with erythromycin or metoclopramide.

Nephropathy
• Compelling evidence has shown the efficacy of ACE inhibitors in reducing the progression of nephropathy in normotensive, microalbuminuric patients 30–300 mg protein loss in 24 hours) in patients with both type 1 and type 2 diabetes.
• The ability of these agents to prevent the onset of microalbuminuria and nephropathy remains to be determined.
• Albuminuria is a marker for cardiovascular disease.
• In hypertensive patients and in normotensive patients with proteinuria, strong consideration should be given to ACE inhibitors and hypertension should be aggressively managed.
• Data suggest that protein restriction may be effective for patients with established nephropathy. See Chapter 33 for a fuller discussion.

Retinopathy
• Retinopathy progresses from background (increased capillary permeability with leakage into vitreous, occlusion of vessels, aneurism formation, and dot and blot hemorrhages) to proliferative (new vessel formation with scarring, macular edema, and retinal detachment).
• Laser photocoagulation has been shown to preserve and improve vision in large trials.
• Patients should have annual retina exams.\textsuperscript{46} Dilated fundoscopic exams have a sensitivity of 80\% compared with stere-oscopnic fundus photography. If a type 1 patient presents with a normal fundus at the time of diagnosis, screening can be deferred for four years, with annual exams thereafter. Patients with any evidence of other complications should be screened yearly.
• Retinopathy is a marker for macrovascular disease.\textsuperscript{47}
• Twenty percent of type 2 diabetic patients have retinopathy on presentation.
• Fifteen percent of patients with background retinopathy develop proliferative disease within 10 years.
• Fifty percent of patients with proliferative disease go blind within five years if not treated.

**Cardiovascular disease**

- The ADA recommends considering aspirin 81–325 mg per day for the primary prevention of heart attack and stroke in diabetics over 30 with other cardiovascular risk factors, including microalbuminuria.

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**Table 14.1 Oral agents for diabetes.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage forms (mg)</th>
<th>Maximum dose</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sulfonylureas</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glyburide (Micronase, Diabeta)</td>
<td>1.25, 2.5, 5</td>
<td>10 mg bid</td>
<td>With meals; bid if &gt; 10 mg/day</td>
</tr>
<tr>
<td>Glipizide (Glucotrol)</td>
<td>5, 10</td>
<td>20 mg bid</td>
<td>Before meals; bid if &gt; 15 mg/day</td>
</tr>
<tr>
<td>Glimepiride (Amaryl)</td>
<td>1, 2, 4</td>
<td>8 mg qd</td>
<td></td>
</tr>
<tr>
<td><strong>Meglitinides</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repaglinide (Prandin)</td>
<td>0.5, 1, 2</td>
<td>4 mg qid</td>
<td>15 minutes before meals</td>
</tr>
<tr>
<td><strong>Biguanides</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin (Glucophage)</td>
<td>500, 625, 750, 850, 1000</td>
<td>850 mg tid</td>
<td>Creatinine must be &lt; 1.4 – 1.5 mg/dl</td>
</tr>
<tr>
<td>Glucophage XR</td>
<td>500, 850, 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Thiazolidinediones</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pioglitazone (Actos)</td>
<td>15, 30, 45</td>
<td>45 mg qd</td>
<td>Monitor LFTs</td>
</tr>
<tr>
<td>Rosiglitazone (Avandia)</td>
<td>2, 4, 8</td>
<td>8 mg qd</td>
<td></td>
</tr>
<tr>
<td><strong>α-Glucosidase inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acarbose (Precose)</td>
<td>50, 100</td>
<td>100 mg tid</td>
<td>With meals; monitor LFTs</td>
</tr>
<tr>
<td>Miglitol (Glyset)</td>
<td>25, 50, 100</td>
<td>100 mg tid</td>
<td></td>
</tr>
</tbody>
</table>


\textsuperscript{47} ETDRS Investigators. Aspirin effects on mortality and morbidity in patients with diabetes mellitus. Early Treatment Diabetic Retinopathy Study Report 14. JAMA 1992;268:1292–300. 3711 patients with diabetic retinopathy were randomized to aspirin or placebo for five years. While retinopathy was not affected, there were 17\% fewer MIs in the aspirin group. 20\% of subjects died or experienced an MI or stroke, showing that retinopathy is a marker for severe vascular disease.
Table 14.2 Human insulins.

<table>
<thead>
<tr>
<th></th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lispro (Humalog)</td>
<td>15 min</td>
<td>30–60 min</td>
<td>3–4 h</td>
</tr>
<tr>
<td>Regular (Humulin R)</td>
<td>30–45 min</td>
<td>2–3 h</td>
<td>5–6 h</td>
</tr>
<tr>
<td>NPH (Humulin N)</td>
<td>2–3 h</td>
<td>6–9 h</td>
<td>12–14 h</td>
</tr>
<tr>
<td>Lente (Humulin L)</td>
<td>3–4 h</td>
<td>4–12 h</td>
<td>12–18 h</td>
</tr>
<tr>
<td>Ultralente (Humulin U)</td>
<td>3–6 h</td>
<td>None</td>
<td>18–24 h</td>
</tr>
</tbody>
</table>

Premixed NPH/regular insulin (70%/30% and 50%/50%) is also available.
Dizziness is a frustrating condition to treat. It is a subjective complaint that cannot be recorded or measured. It can be caused by several different pathophysiological mechanisms. Patients are often frustrated that physicians are unable to understand what they are feeling and provide a specific diagnosis. There are few well conducted studies upon which to base diagnosis and treatment recommendations. Most published information consists of expert opinion.

**Epidemiology**
- Dizziness is a common complaint in the primary care setting. There were more than 7 million visits for dizziness in 1997.¹
- Prevalence increases with age. Approximately 30% of patients over the age of 65 complain of dizziness severe enough to see a doctor, take a medication, or interfere with daily activities.² Women tend to experience dizziness more than men.
- Patients with dizziness often have multiple etiologies for their symptoms, particularly elderly patients.
- Most data on the etiology of dizziness within the community are of poor quality due to biases in patient selection, referral patterns, subjective diagnostic criteria, and numerous exclusion criteria. However, most³–⁶ but not all⁷ point to benign positional vertigo (BPV) as the leading cause of dizziness in the community.

**Pathophysiology**
- Balance is maintained by input from the visual, proprioceptive, and vestibular systems to the vestibular nuclei and cerebellum.
- Unequal neural activity from the ears to the vestibular nuclei causes the sensation of vertigo.
- Connections to extraocular muscles are responsible for nystagmus.
- Stimuli from the vestibular nuclei to the vagus nerve cause nausea and vomiting.
- There is inhibitory cortical input to the cerebellum and vestibular nuclei. This is why an ice skater can be trained not to become dizzy when spinning.

**Diagnosis**
**Differential diagnosis**
**Overview**
- The initial step in diagnosis is to categorize the clinical symptoms as vertigo, dysequilibrium, or presyncope. These symptoms generally have organic etiologies.
Symptoms that do not fall into these three categories usually have non-organic causes. Psychogenic dizziness is considered a diagnosis of exclusion.

The Dizziness Handicap Inventory (see Box 15.1) can be used to assess how significantly a patient is impacted by dizziness as well as a measure of treatment effectiveness.

Vertigo

- The illusion of false motion. The patient has the sensation of moving (spinning, tumbling, tilting) in the room or the room appears to be moving around the patient.
- The sensation of vertigo is due to an asymmetry of neural activity between the right and left vestibular nuclei. The lesion may be peripheral (inner ear) or central (brainstem or cerebellum).


Each “yes” answer gets 4 points. A “sometimes” answer gets 2 points. A “no” answer gets 0 points. A score of 100 indicates severe self perceived impairment, while a score of 0 indicates no handicap. If treatment decreases the score by 18 points, it has made a significant impact on the patient’s quality of life.

- Does looking up increase your symptoms?
- Are you frustrated by your symptoms?
- Do you restrict your travel due to your symptoms?
- Does walking down the aisle of a store worsen your symptoms?
- Any difficulty getting in and out of bed?
- Do you restrict your social activities because of your symptoms?
- Are performing high exertion activities (dancing, cleaning) a problem?
- Any difficulty reading?
- Are you embarrassed in front of others because of your symptoms?
- Are you afraid to leave your home?
- Do your symptoms worsen with quick movements of the head?
- Do you avoid heights?
- Does turning in bed make your symptoms worse?
- Do you have trouble with strenuous yard work?
- Are you afraid you appear drunk?
- Is it difficult to go for a walk alone?
- Does walking down a sidewalk worsen your symptoms?
- Is it difficult to concentrate?
- Is it difficult to walk around in the dark?
- Are you afraid to be at home alone?
- Do you feel handicapped because of your symptoms?
- Has this placed a strain on your relationships?
- Do you feel depressed?
- Does your problem interfere with your responsibilities?
- Does bending over increase your symptoms?
• Associated symptoms include nausea, vomiting, diaphoresis, and nystagmus.
• Vertigo is worsened by head movement.
• Vertigo is always a temporary problem because neurochemical changes occur in the brainstem to compensate and adapt to the symptoms.
• Common etiologies include BPV, vestibular neuronitis, Meniere’s disease, and migraines.
• Rare, but serious, etiologies include brainstem or cerebellar stroke. Acoustic neuromas usually present with unsteadiness rather than true vertigo.

**Dysequilibrium**
• A sensation of imbalance, usually accompanied by a fear of falling. Symptoms occur when walking, but not when sitting or lying down.
• With age, the ability of the cerebellum to process sensory input slows and there is difficulty walking in the dark or on uneven ground.
• Motor systems are also affected; thus, these patients have trouble regaining their balance, resulting in a high incidence of falls.
• Etiologies include: peripheral neuropathies, poor vision, arthritis, Parkinson’s disease, deconditioning, vitamin B12 deficiency, myelopathy, and medications (benzodiazepines, anticholinergics, haloperidol, lithium, phenytoin, etc.).

**Presyncope**
• The feeling that one is about to faint. Symptoms include lightheadedness, nausea, diaphoresis, a buzzing sensation, constriction of the visual field, rubbery legs.
• Vascular causes include vasovagal (micturition, coughing, defecation), orthostatic hypotension, carotid sinus pressure, subclavian steal syndrome, and vertebrobasilar insufficiency.
• Cardiac causes include arrhythmias, AV conduction abnormalities, aortic stenosis, mitral insufficiency, and hypertrophic cardiomyopathy.
• Neurologic causes include seizure, normal pressure hydrocephalus, and cervical spondylosis.
• Other causes: medication, hypoxia, hypoglycemia, and anemia.

**Psychogenic dizziness**
• The generally accepted definition is dizziness that is not associated with true vertigo, dysequilibrium, or presyncope.
• It can be associated with anxiety, phobia, or other psychiatric symptoms and can often be replicated by hyperventilation.

**History**

**General questions**
• Age ≥79 increases the likelihood that the etiology of the dizziness is presyncope.

11 Herr RD, Zun L, Matthews JJ. A directed approach to the dizzy patient. Ann Emerg Med 1989;18:664–72. 124 dizzy patients who presented to an emergency room were followed for one month, looking for serious causes of dizziness (seizure, TIA, stroke, arrhythmia, medication toxicity). Absence of vertigo, age >69, or presence of neurological deficit had a sensitivity of 87% and specificity of 42% for serious cause. The study was limited by high exclusion rates and limited follow up. The clinical prediction rule was not validated in a separate population. It is, however, the only information we have on criteria for serious dizziness.
Cardiac disease, stroke, and diabetes increase the possibility of presyncope dizziness.

Peripheral neuropathy increases the possibility of a disequilibrium problem.

Anxiety and depression increase the possibility of psychogenic dizziness.

Medications: salicylates, aminoglycosides, antihypertensives, anticonvulsants, oral hypoglycemics, benzodiazepines.  

Description of the syndrome (see above).

Timing and duration

Episodic, lasting for seconds at a time, less than three months: BPV

Episodic, lasting for hours, slowly progressive: Meniere’s disease

Continuous, lasting 1–2 weeks: vestibular neuronitis

Prolonged course: central processes

Precipitants

Change in head position: BPV

Rising from a lying position: orthostasis

Exertion: cardiac or vascular

Coughing, urination, defecation: vasovagal presyncope

Medication use: vertigo, presyncope, disequilibrium

Walking on uneven ground or at night: dysequilibrium

Early morning vertigo: peripheral rather than central vestibular disorders

Anxiety provoking event: psychogenic

Associated symptoms

Recent viral illness: vestibular neuronitis or labyrinthitis

Hearing loss: otosclerosis

Hearing loss, fullness in ear, roaring tinnitus: Meniere’s disease

Progressive asymmetric hearing loss, fullness in ear, tinnitus, unsteadiness (rather than true vertigo): acoustic neuroma

Brainstem neurological symptoms: stroke

Palpitations, chest pain: cardiac etiology

Physical exam

General exam

Blood pressure, orthostatics, cardiac exam

Hearing (conductive vs sensorineural hearing loss), tympanic membrane integrity

Craniat nerves, especially V (trigeminal), VI (abducens), VII (facial), VIII (vestibulocochlear), IX (glossopharyngeal)

Cerebellar function: finger to nose, heel to shin, repetitive movements and gait and Romberg test

Peripheral sensory and motor function

Nystagmus

Spontaneous horizontal nystagmus with or without a rotational component is typical of peripheral vestibular


Drugs causing dizziness

The aminoglycosides are ototoxic, especially in the presence of renal insufficiency. They are concentrated within the endolymph fluid in the inner ear and damage the end organs. Gentamicin is mainly vestibulotoxic while amikacin is mainly cochleotoxic. In some cases streptomycin is actually used to ablate the peripheral vestibular organs as a treatment for intractable vertigo.

The loop diuretics furosemide and ethacrynic acid are cochleotoxic and can potentiate the effects of aminoglycosides.

Salicylates at high cumulative doses can cause tinnitus, hearing loss, imbalance, and rarely vertigo.

Anticonvulsants (phenytoin, phenobarbital, carbamazepine) and psychotropic drugs (tricyclics, haloperidol, benzodiazepines, lithium) can cause ataxia and dysequilibrium.

Nystagmus: rhythmic oscillation of the eyes that results from altered input from the vestibular nuclei to the extraocular muscles. If nystagmus occurs at extreme lateral gaze, it is not considered pathologic. Spontaneous nystagmus is not affected by head position. Positional nystagmus is induced by actions such as the Dix-Hallpike maneuver.
disorders. The direction of the nystagmus is unaffected by changing the direction of gaze. Nystagmus of peripheral origin is suppressed by visual fixation, therefore often missed on physical exam.

- Central vestibular disorders can cause all types and combinations of nystagmus, although they are classically associated with pure vertical or pure rotational nystagmus.

**Romberg test**

- Peripheral vestibular disorders cause patients to lean toward the lesion, but they are able to walk.
- Central vestibular disorders cause severe postural instability and patients will often fall when attempting to walk.

**Additional maneuvers**

- Dix-Hallpike maneuver to induce BPV and nystagmus (see BPV below).
- Hyperventilation test to induce psychogenic dizziness.

**Imaging**

- For most patients with dizziness, imaging is of little value because the vast majority of causes can be identified clinically.
- Imaging is used to rule out the rare but serious causes of dizziness: acoustic neuroma, brainstem stroke and cerebellar stroke.
- If there is progressive asymmetric hearing loss with tinnitus, cranial nerve palsies or nystagmus, consider acoustic neuroma and image the patient for a cerebellopontine mass.
- If there is dizziness with neurologic findings (ataxia, dysarthria, diplopia, hemiparesis) in an elderly patient with atherosclerotic risk factors, consider brainstem or cerebellar stroke as the cause.
- MRI is the test of choice to visualize the brainstem.

**Common vestibular disorders**

**Benign positional vertigo**

- Hypothesis: BPV occurs when otoliths loosen and enter the posterior semicircular canal. This disturbs endolymphatic flow and nerve conduction to the brainstem.
- Most cases are idiopathic. Identifiable causes include head trauma and postvestibular neuronitis.

**Symptoms**

- Sudden onset of vertigo that is provoked by changes in head position. Patients can complain of vertigo when rolling over in bed or bending forward.
- Usually lasts for seconds.
- Usually present for <3 months, but recurrences and remissions can persist for years.
- Characterized by fatiguability: symptoms decrease on repeated placement of head in the inciting position.
- Associated with nausea and vomiting.

---

**Romberg test:** the patient stands with both feet together, arms folded or at the sides. The examiner is positioned to support the patient in the event of unsteadiness or a fall. The patient closes eyes and attempts to maintain balance.

**Hyperventilation test:** ask the patient to breathe rapidly for two minutes. If this induces symptoms of dizziness, it is suggestive of psychogenic dizziness, provided other diagnoses have been excluded. The usefulness of this test is questionable. In a study by Kroenke et al, 21 patients had dizziness associated with hyperventilation but only one patient primarily had psychogenic dizziness.

**Dix-Hallpike maneuver:** the patient’s head is held in the examiner’s hands while the patient is seated lengthwise on the exam table with the knees extended. Then, in 1–2 seconds, the patient’s head is brought below the head of the exam table and tilted 30° to the right. The maneuver is then repeated with the head tilted to the left. One of these positions should elicit the patient’s symptoms and associated nystagmus. The nystagmus is usually mixed torsional and vertical. It begins with a 1–2 second latency and lasts 10–20 seconds.
Diagnosis
- History
- Dix-Hallpike test

Treatment
- Habituation: symptoms will resolve much more rapidly if the head is repeatedly put in the inciting position. The brain adapts to the asymmetric signals.
- Symptoms usually resolve within three months but if patients avoid the inciting position recovery could take longer.
- The Epley maneuver attempts to reposition the loose otoliths from the posterior semicircular canal back to the utricle.
- Vestibular suppressants can reduce symptoms, but can actually hamper the central nervous system’s adaptation to the peripheral vestibular abnormality when used for more than 1–2 weeks. Side effects include lethargy and worsening balance which are especially of concern given that the symptoms are episodic.
- Meclizine is a weak centrally acting antihistamine whose exact mechanism of action is unknown.
- Phenothiazines have a weak antihistamine effect and also decrease nausea. Dystonic reactions can occur, especially in the young and elderly.
- Scopolamine and atropine are anticholinergics that work by decreasing stimulation of the vestibular nuclei. Very effective for motion sickness. Side effects include drowsiness, dry mouth, dilated pupils, and tachycardia.
- Benzodiazepines inhibit the resting activity of the vestibular nuclei and the reticular activating system. Their utility in the treatment of BPV is controversial. Side effects include drowsiness and dependence.
- Neurectomy is reserved for intractable symptoms. Nerve fibers of cranial nerve VIII to the posterior semicircular canal are resected.

Vestibular neuronitis
- Caused by acute injury or inflammation of the semicircular canals and vestibular nerves

Symptoms
- Sudden, severe, continuous vertigo
- Often follows upper respiratory viral illness.
- Typically begins over a period of hours and lasts for <1 week, though residual imbalance or dizziness may last for weeks to months.
- Exacerbated by head movements.
- Accompanied by nausea and vomiting.
- If there is loss of hearing, it implies damage to the entire labyrinth including the cochlea (acute labyrinthitis).
Diagnosis
- History
- Head impulse test\textsuperscript{20}
- Nystagmus, suggesting a peripheral disorder

Treatment
- Vestibular suppressants, particularly meclizine, are effective. Patients generally require intensive treatment because the continuous nature of the vertigo can severely affect quality of life.

Meniere’s disease
The slow accumulation of endolymphatic fluid within the ear resulting in hydrops of the inner ear.\textsuperscript{21}

Symptoms
- Episodic vertigo which reaches maximum intensity in minutes and then subsides slowly over hours.
- Tinnitus, frequently described as a roar.
- Fullness in the affected ear.
- Progressive sensorineural hearing loss, notably at low frequencies.
- Episodic symptoms progress insidiously to permanent hearing loss, unless early diagnosis is made.
- Usually unilateral, but 30\% have bilateral involvement.

Diagnosis
- History
- Exclude other diagnoses, particularly acoustic neuroma.
- Audiometry for low frequency losses.

Treatment
- Vestibular suppressants for symptom relief during acute attacks
- Dietary restrictions of sodium, caffeine, alcohol, and tobacco
- Diuretics
- Surgery for patients with severe refractory symptoms.
- Endolymphatic–mastoid shunt to drain the accumulating fluid. Effectiveness is not clear.
- Neurectomy to resect part of cranial nerve VIII.
- Complete labyrinthectomy if all hearing is lost.

Acoustic neuroma (Schwannoma)
- A benign tumor of the nerve sheath cells, or Schwann cells, surrounding the auditory nerve.
- Usually occurs at the cerebellopontine angle.

Symptoms\textsuperscript{22}
- Progressive asymmetric hearing loss due to gradual compression of the auditory nerve. The vestibular portion of the auditory nerve is affected, but vertigo is rarely perceived because the brain adapts to the slowly developing vertiginous symptoms. The patient may instead describe unsteadiness.

\textsuperscript{20} Head impulse test: the patient’s head is turned about the horizontal axis rapidly 15° to one side. Observe whether the patient is able to keep fixating on a distant object. Then the head is turned to the other side and the patient is checked for fixation. If the patient has lost unilateral function of the semicircular canals, the vestibular-ocular reflex will fail on that side. Thus, the patient will have difficulty fixating on a target when the head is turned to the affected side and will need a rapid eye movement to regain fixation. When this test is positive, it suggests a vestibular neuronitis.


Palsies of cranial nerves V–IX as tumor eventually compresses the brainstem.

Acute vertigo signals hemorrhage into the tumor.

**Diagnosis**
- History
- MRI

**Treatment**
- Surgical removal

**Brainstem stroke (Vertebrobasilar insufficiency)**
- Occlusion of the basilar artery causes ischemia of the vestibular nuclei in the pons and the auditory nerve.
- Risk factors include long standing diabetes, smoking, hypertension, and atherosclerosis.

**Symptoms**
- Vertigo can occur if the vestibular nuclei are affected.23
- Dizziness, dysarthria, diplopia, hemiparesis, ataxia, headache, and hearing loss are more common.
- Nystagmus not of peripheral origin (for example, vertical, bidirectional, not suppressed by visual fixation).

**Diagnosis**
- History
- MRI

**Treatment**
- Supportive
- Control of risk factors
- Antiplatelet agents (aspirin, dipyridamole, clopidogrel, possibly warfarin)

**Cerebellar stroke**
- Occlusion of posterior inferior, anterior inferior, or superior cerebellar arteries.
- A cerebellar infarction may evolve into hemorrhage, which could be life threatening secondary to mass effect compressing the brainstem.

**Symptoms**23,24
- Sudden imbalance
- Sudden vertigo
- Extreme difficulty in standing and walking.
- Cranial nerve palsies (since cerebellar arteries also supply the pons)
- Isolated vertigo and deafness can occur if there is a localized infarct of the internal auditory artery branch of the anterior inferior cerebellar artery.
- Nystagmus not of peripheral origin (for example, vertical, bidirectional, not suppressed by visual fixation).

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23 Fisher CM. Vertigo in cerebrovascular disease. Arch Otolaryngol 1967; 85:529–34. Dizziness was an extremely rare complaint in patients with an anterior circulation stroke, but was a cardinal sign of a brainstem stroke. Other associated symptoms of brainstem infarction included diplopia and dysarthria.

Diagnosis
- History
- Negative head impulse test
- CT or MRI

Treatment
- Supportive
- Control of risk factors
- Antiplatelet agents (aspirin, persantine, clopidogrel, possibly warfarin)

Table 15.1  Common medications for dizziness.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage forms (mg)</th>
<th>Usual dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antihistamines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meclizine (Antivert)</td>
<td>12.5/25/50 mg tabs</td>
<td>Motion sickness: 25–50 mg 1h prior to departure, repeat q24 h prn</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute neuronitis: 25–100 mg per day in divided doses</td>
</tr>
<tr>
<td>Dimenhydrinate (Dramamine)</td>
<td>50 mg tabs</td>
<td>Motion sickness: 50–100 mg PO q4–6 h starting 1h prior to departure</td>
</tr>
<tr>
<td><strong>Phenothiazines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prochlorperazine (Compazine)</td>
<td>5, 10 mg tabs</td>
<td>5–10 mg PO tid or qid</td>
</tr>
<tr>
<td></td>
<td>2.5, 5, 10 mg suppositories</td>
<td>25 mg PR bid</td>
</tr>
<tr>
<td>Promethazine (Phenergan)</td>
<td>12.5/25/50 mg tabs</td>
<td>25 mg PO bid</td>
</tr>
<tr>
<td><strong>Anticholinergics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scopolamine (Transderm Scop)</td>
<td>1.5 mg transdermal patch</td>
<td>Motion sickness: 1 patch behind ear 4h prior to departure; lasts 3 days</td>
</tr>
</tbody>
</table>
16 Domestic violence
Allen Keller and Suzanne Groisser

Introduction
- Domestic violence against women (also known as partner abuse, spouse abuse, or battering) is a serious nationwide health problem.
- Domestic violence is characterized as a pattern of coercive behaviors that may include repeated physical abuse, psychological abuse, sexual assaults, progressive social isolation, and intimidation.
- Primary care physicians have an essential role to play in identifying, caring for, and counseling victims of domestic violence.
- Battered women often suffer from repeated injuries, medical problems, and mental health problems. By recognizing and treating the effects of domestic violence and by providing appropriate counseling and referrals, primary care physicians can make significant contributions to improving women's health.

Epidemiology

Prevalence
- Two to four million women are physically abused every year in the US by their spouses or partners. An estimated 10–30% of all women will be assaulted by a partner in their lifetime.
- Domestic violence results in more injuries to women than auto accidents, muggings, and rapes combined.
- In primary care settings, the prevalence of women suffering from domestic violence in the past year is estimated to be 5–14% and 20–28% in their adult life. Women are more likely to be assaulted, raped, or killed by a current or former partner than by all other types of assailants combined.

Risk factors
- Domestic violence is prevalent in all racial, educational, geographical, and socioeconomic segments of society.
- Domestic violence is particularly common during pregnancy, with prevalence estimates ranging from 16 to 37%.

Diagnosis

Clinical characteristics
- In addition to acute physical trauma, domestic violence is associated with many physical and psychological sequelae, including somatic symptoms, headaches, chronic abdominal pain, pelvic pain, musculoskeletal pain, anxiety, and depression.
- Alcohol and drug addiction and eating disorders are other health related sequelae of short and long term abuse.

The US Department of Justice estimates that 95% of assaults on spouses or ex-spouses are committed by men against women. Bureau of Justice Statistics. Report to the Nation on Crime and Justice. Washington, DC: Dept. of Justice, 1983.
4 Sassetti MR. Domestic violence. Primary Care 1993;20:289–305.
5 McCauley J, Kern DE, Kolodner K et al. The "battering syndrome": prevalence and clinical characteristics of domestic violence in primary care internal medicine practices. Ann Intern Med 1995;123:737–46. This is the largest study of domestic violence in a primary care setting, with nearly 2000 respondents. The authors found that women who were currently being abused had more physical symptoms; higher levels of depression, anxiety, and somatization; and lower levels of self esteem than women who were not being abused.
9 Drossman DA, Talley NJ, Leserman J, Olden KW, Barreiro MA. Sexual and physical abuse and gastrointestinal illness: review and recommendations. Ann...
Chronic illnesses such as asthma, seizure disorders, diabetes, arthritis, hypertension, and heart disease may be exacerbated or poorly controlled in women who are being abused.⁷

The interviewing process
- All female patients should be routinely asked about domestic violence. Physicians should be particularly motivated to inquire about the possibility of current domestic violence when a woman presents with multiple somatic symptoms or emotional distress.¹⁰
- Such questions may be included in the history of the present illness, past medical history, or social history as appropriate.
- Questions about domestic violence should be asked in a simple, direct, non-judgmental way. For example: “Because violence is so common in many women’s lives, I’ve begun to ask about it routinely. Are you in a relationship in which you have been physically hurt or threatened by your partner? Have you ever been in such a relationship? Do you ever feel afraid of your partner?” If the patient answers “yes”:
  1. Encourage her to talk about it. For example: “Would you like to talk about what happened to you?”
  2. Listen non-judgmentally.
  3. Validate her experience. Examples:
     “You are not alone.”
     “You are not to blame.”
     “You do not deserve to be treated this way.”
     “What happened to you is a crime.”
     “Help is available to you.”
- Interview the woman alone without her partner present.

Documentation
- If a woman acknowledges a recent history of abuse, record an account of the abuse using the patient’s own words as much as possible (“The patient states...”).¹¹
- Record all pertinent physical findings. Include a detailed description of the injuries, including type, number, size, location, and explanations given. Also, include an opinion of whether the injuries are consistent with the patient’s report of what occurred.
- Common types of injury include contusions, abrasions, and minor lacerations, as well as fractures and sprains.¹²
- If a woman denies abuse but you strongly suspect it, document your opinion and let her know there are resources available to her, should she choose to pursue such options in the future. Make a follow up appointment to see her.

Treatment
Counseling and referral
- If the woman is currently in an abusive relationship, assess the patient’s safety before she leaves the medical setting at

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"Intern Med 1995;123:782–94. The authors agreed with existing data on the association between gastrointestinal illness and a history of abuse.

"10 Although many women who are victims of domestic violence will not volunteer any information, they will discuss it if asked simple, direct questions in a non-judgmental way. In one study, 78% of patients surveyed favored routine inquiry about domestic violence and 90% of patients felt physicians could be helpful with such problems. Friedman L, Samet JH, Roberts MS, Hudlin M, Hans P. Inquiry about victimization experiences: a survey of patient preferences and physician practices. Arch Intern Med 1992;152:1186–90.

"11 Thorough, well documented medical records can provide concrete evidence of violence; they may prove crucial to the outcome of any legal case and to the prevention of further abuse.

"12 Photographs of injuries can serve as important documentation and are invaluable as evidence."
each visit. Specifically, find out if she is afraid to go home. Has there been an increase in the frequency or severity of violence? Have there been threats of homicide or suicide? Have there been threats to her children? Is there a gun present?  

- Offer her written and verbal information about the formal network of domestic violence services available.  
- Explore informal resources and supports to which she may have access such as friends, neighbors, family, and church and social groups.  
- If the woman is willing, refer her for individual counseling. Couples counseling or family intervention is generally contraindicated in the presence of domestic violence. Attempts to implement family therapy in the presence of ongoing violence may increase the risk of serious harm.  

Legal issues  
- It is important that victims of domestic violence know that they can seek legal protection against their abusers. In local courts, the victim may seek an order of protection from a judge. This orders the abuser to stay away from her home, school, and place of work and to abstain from any further abusive behavior.  
- If a patient is physically or sexually abused or threatened with violence, a complaint can be made with her local police precinct and the abuser can be prosecuted in a criminal court. In a family court, the victim may also seek custody of her children and child support.  
- A physician is not under legal obligation to report adult domestic violence in most states. Child abuse is a reportable offense.  

13 If the patient states that it is not safe for her to go home, assistance must be provided in finding her emergency shelter. Many localities have domestic violence hotlines and shelters.  
14 Remember that it may be dangerous for the woman to have written information in her possession. Do not insist if she is reluctant to accept. Consider writing the phone numbers on a prescription blank or an appointment card.
Dyspepsia, peptic ulcer disease, and gastroesophageal reflux disease
Mark D Schwartz

**Epidemiology**

**Dyspepsia**
- The constellation of symptoms may include gas, bloating, nausea, vomiting, and early satiety.
- Twenty-six percent of the adult population complain of dyspepsia each year and 10% experience heartburn daily.¹
- In 1997 there were 187,850,000 ambulatory care visits in the US for stomach and abdominal pain, cramps, and spasms. Dyspepsia was the third most common symptomatic reason (after cough and sore throat) for visiting an ambulatory care setting.²

**Peptic ulcer disease (PUD)**
- The US prevalence of PUD is 1% and lifetime cumulative incidence is 10% for men and 4% for women. Prevalence and incidence of PUD have declined for the last two decades, probably due to decreasing rates of *H. pylori* infection.
- There are 400,000 new cases of PUD each year.
- Duodenal ulcers are twice as common in men as in women and 1.5 times as common as gastric ulcers.
- Peak incidence is in the 40s for men and 50s to 60s for women.

**PUD as a chronic disease**
- Up to 90% of patients with duodenal ulcers will suffer a recurrence (many asymptomatic) within one year if not given maintenance therapy and if *H. pylori* is not eradicated.³
- Complications of PUD include bleeding or perforation in 1–3% per year.
- One to three percent of gastric ulcers coincide with gastric carcinoma.
- Risk factors for PUD beyond *H. pylori* include use of aspirin and NSAIDs, male sex, family history, stress, smoking, chronic renal failure, chronic obstructive pulmonary disease, and alcoholism.

**Helicobacter pylori (H. pylori)**
- A Gramnegative, urease producing bacterium that colonizes gastric mucosa and produces chronic, superficial, antral gastritis.

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• One of the world’s most common bacterial pathogens, with a prevalence in the general US population of 40% and 70–80% in the developing world.\(^4\)
• Prevalence is 50% by age 50 and is highest among African and Latino-Americans.
• Incidence in the developed world has decreased markedly with improved sanitary conditions, with new infection rates now at \(<0.5\%\) per year. Therefore, most current infections reflect exposure during childhood.
• The consensus is that \(H.\, pylori\) is the major cause of chronic gastritis and duodenal and gastric ulcers.
• Koch’s postulates have been met for gastritis and the evidence is overwhelming for PUD.
• Over 95% of patients with PUD are infected with \(H.\, pylori\).
• For non-ulcer dyspepsia, however, the prevalence of \(H.\, pylori\) is no higher than in the general population.
• For gastric carcinoma, non-Hodgkin’s lymphoma, and mucosa associated lymphoid tissue (MALT) lymphoma, there is evidence of a strong association with \(H.\, pylori\) infection.
• Causal evidence is strongest for MALT lymphomas which have completely disappeared with eradication of \(H.\, pylori\).\(^5\)

**Gastroesophageal reflux disease (GERD)**\(^6\)
• Ten percent of the US population have daily heartburn.
• Barrett’s esophagus – replacement of the squamous epithelium of the esophagus by columnar epithelium – develops in 10–15% of patients with chronic GERD. Barrett’s esophagus is associated with an increased risk of esophageal adenocarcinoma.

**Diagnosis**

**Non-ulcer dyspepsia**
• Non-ulcer dyspepsia is a common clinical syndrome with varied presentation and multifactorial etiology.
• Is defined as chronic dyspeptic symptoms (episodic or persistent pain or discomfort localized to the epigastrium or upper abdomen) in which clinical evaluation and studies have failed to reveal a pathological cause.\(^7\) It is, therefore, a diagnosis of exclusion.
• Patients can be grouped by symptom pattern as ulcer-like, dysmotility-like, and reflux-like, but there is much overlap.
• Differential diagnosis includes PUD (5–30%), irritable bowel syndrome (23%), gastroesophageal reflux (22%), and chronic biliary or pancreatic disorders (5–10%).\(^8\)

**Peptic ulcer disease**
• Diagnosing PUD by clinical evaluation alone is challenging.
• Textbook descriptions of “classic” presentations have not been supported by evidence.
• The best study to date found four independent clinical predictors.\(^9\)

\(^4\) NIH Consensus Conference. *Helicobacter pylori in peptic ulcer disease.* JAMA 1994;272:65–9. This important summary received considerable media attention and increased public awareness of \(H.\, pylori\).

**Koch’s postulates**
1. The micro-organism in question must always be present in diseased hosts.
2. The micro-organism must be isolated from the diseased host and grown in pure culture.
3. Micro-organisms obtained from the pure culture, when injected into a healthy susceptible host, must produce the disease in that host.
4. Micro-organisms must be isolated from the experimentally infected host, grown in pure culture, and compared with the micro-organisms in the original culture.


• If any one of these findings is present, the decision rule has a sensitivity of 95%, specificity of 30%, positive LR of 1.4, and negative LR of 0.2.
• The high sensitivity may help to rule out the diagnosis; in the absence of any of these findings the probability of PUD drops from 10% (baseline prevalence) to 2% (probability after history).
• In a study of 659 patients sent for UGI in an urban health center, the independent predictors of an abnormal radiograph finding were: age >45 years, male sex, history of PUD, pain at night, and lack of bowel symptoms.10
• Physical examination is most helpful in exploring non-peptic acid disorders in the differential diagnosis. Localized epigastric tenderness is common and non-specific. Examination of stool for occult bleeding is important to guide prognosis and further diagnostic investigation.
• The two studies for diagnosing PUD are double-contrast upper gastrointestinal radiography (UGI) and esophagogastroduodenoscopy (EGD). Operating characteristics of these tests in the diagnosis of duodenal and gastric ulcers are as follows.

### Operating Characteristics of UGI and EGD

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>+LR</th>
<th>−LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>UGI series</td>
<td>85%</td>
<td>95%</td>
<td>17</td>
<td>.16</td>
</tr>
<tr>
<td>EGD</td>
<td>95%</td>
<td>99%</td>
<td>95</td>
<td>.05</td>
</tr>
</tbody>
</table>

• The higher sensitivity of EGD makes it a better test to rule out PUD, but the difference is not as large as it first appears. If the pretest probability is 10%, then the post-test probability is 1.5% after a normal UGI and 0.5% after a normal EGD.
• In reality, choice of test is often dictated by availability.

### Helicobacter pylori

There are five methods for diagnosing *H. pylori* infection.

#### Diagnostic Tests for *H. pylori*

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Relative cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-invasive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serology</td>
<td>95%</td>
<td>86–95%</td>
<td>$</td>
</tr>
<tr>
<td>Breath test</td>
<td>90–95%</td>
<td>98–100%</td>
<td>$$</td>
</tr>
<tr>
<td>Invasive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLO test</td>
<td>90–98%</td>
<td>90–98%</td>
<td>$$$$</td>
</tr>
<tr>
<td>Histology</td>
<td>93–99%</td>
<td>95–99%</td>
<td>$$$$$</td>
</tr>
<tr>
<td>Culture</td>
<td>70–95%</td>
<td>100%</td>
<td>$$$$$</td>
</tr>
</tbody>
</table>

10 Schwartz M, Lee E, Lipkin M, Yedidia M. Dyspepsia in the inner city: predictors of an abnormal UGI. J Gen Intern Med 1997;12:57. In this study at Gouverneur Diagnostic and Treatment Center in New York City, about 90% of patients had normal or unimportant findings on UGI series. If the test/no test threshold is much below 10%, then it would be prudent to evaluate most dyspeptic patients with UGI or EGD.


The serology test is an enzyme linked immunosorbent assay (ELISA) for IgG antibodies to *H. pylori*. Like most serology tests, it cannot distinguish between active infection and serologic scar. A quick, inexpensive, office based qualitative test for *H. pylori* antibodies is also available.

The urea breath test is based on ingesting carbon labeled urea, which is hydrolyzed by *H. pylori* urease to labeled bicarbonate and exhaled as labeled CO₂, which can be measured. This test is quick, inexpensive, and highly accurate – the ideal test for the presence and eradication of *H. pylori*.

The invasive tests all require EGD and are therefore much more expensive. The Campylobacter-like organism (CLO) test is a rapid, pH based, urease biopsy test. False negatives result from biopsy sampling errors. For patients requiring EGD, the CLO is the preferred test.

Histology is highly sensitive and allows pathologic examination of the mucosa. It is reasonable to send histology only if the CLO test is negative.

Culture is insensitive because the organism is fastidious. It should only be used when antibiotic sensitivities are needed.

**GERD**

- Heartburn (tight, burning sensation radiating from the xyphoid process to the neck) and acid regurgitation are typical symptoms.¹³
- Symptoms are exacerbated by fatty foods, caffeine, and recumbent position.
- GERD can mimic or exacerbate other diseases. Hoarseness, chronic cough, dental erosions, and asthma exacerbation may all occur with or without typical symptoms of GERD. Heartburn can mimic atypical angina.

**Diagnostic testing**⁶

- In the approach to patients with heartburn, a reasonable first step is an empiric trial of a proton pump inhibitor. In one study, high dose omeprazole (40 mg twice a day for seven days) was used as a diagnostic test.¹⁴ Relief of symptoms by 75% counted as a positive result and was 83% sensitive for GERD. Further diagnostic testing should be considered in patients who do not respond to an empiric trial.
- Barium radiography has varying sensitivity, depending on severity of disease, and is abnormal in 20% of patients without disease (80% specific).
- On upper endoscopy, only 25% of patients with GERD have macroscopic changes of esophagitis by visual inspection and only 50% have esophagitis on biopsy. Because of the risk of Barrett’s esophagus, endoscopy should be considered in patients with severe or treatment resistant disease.
- Twenty-four hour ambulatory intravesophageal pH testing may be up to 96% sensitive and 96% specific.

---


Accuracy of Typical Symptoms in Diagnosis of GERD

<table>
<thead>
<tr>
<th>Presence of a symptom</th>
<th>Sens (%)</th>
<th>Spec (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid regurgitation</td>
<td>60</td>
<td>52</td>
</tr>
<tr>
<td>Heartburn</td>
<td>68</td>
<td>52</td>
</tr>
<tr>
<td>Retrosternal burning</td>
<td>61</td>
<td>51</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Presence of a clearly dominant symptom</th>
<th>Sens (%)</th>
<th>Spec (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid Regurgitation</td>
<td>6</td>
<td>95</td>
</tr>
<tr>
<td>Heartburn</td>
<td>38</td>
<td>89</td>
</tr>
<tr>
<td>Retrosternal burning</td>
<td>14</td>
<td>84</td>
</tr>
</tbody>
</table>

¹⁴ Schindlbeck NE, Klauser AG, Voderholzer WA, Müller-Lissner SA. Empiric therapy for gastroesophageal reflux disease. Arch Intern Med 1995; 155:1808-120. The sensitivity of this test was 83% with omeprazole 40 mg bid and only 27% with omeprazole 40 mg qd.
Treatment
Non-ulcer dyspepsia
Two recent practice guidelines suggest the following approach to a patient with undiagnosed dyspepsia.15,16
• First, consider other causes including cardiac, hepatobiliary, and medication induced etiologies. If present, treat the other cause.
• If there is no other apparent cause, assess whether the patient is >50 years old or alarm features are present. Alarm features – vomiting, bleeding or anemia, unexplained weight loss, abdominal mass, and dysphagia – are indications for EGD.
• If the patient is <50 and without alarm features, evaluate for aspirin or NSAID use. Discontinue aspirin or any NSAIDs or switch to acetaminophen or a COX-2 inhibitor and reassess the patient.
• If no aspirin or NSAIDs are being used, assess whether the predominant symptom is heartburn (a rising burning sensation) or regurgitation. If yes, treat as GERD with a proton pump inhibitor or H2 receptor blocker for four weeks and reassess the patient. Investigate with EGD if there are persistent or recurrent reflux symptoms.
• If the predominant symptom is not heartburn or regurgitation, consider one of the following three strategies:
  1. empiric anti-ulcer treatment
  2. evaluation with UGI or EGD
  3. test and treat for H. pylori.

Empiric anti-ulcer treatment
• A 4–6 week trial of therapy with antacids or an H2 receptor antagonist (H2RA).
• If symptoms do not respond in 2–4 weeks or if symptoms recur after treatment is stopped at six weeks, further work up should be done.

Evaluation with UGI or EGD
• Advised in higher risk patients – those over 50 or those with the predictive diagnostic features noted above.

Non-invasive testing for H. pylori and antibiotics for infected patients (“test and treat” strategy)
• Only 15–30% of H. pylori infected patients with dyspepsia will have PUD.
• Eradication of H. pylori in patients with non-ulcer dyspepsia (the other 70–85%) has not been shown to be more effective than placebo in improving symptoms in blinded, randomized trials.
• The best approach is still unclear. Testing and treating H. pylori is initially the most cost effective, but since many patients ultimately need further evaluation, UGI or EGD has been shown to be most cost effective over the longer term.17 Empiric anti-ulcer treatment is a rational approach unless the patient is at high risk, as defined above.

17 Bytzer P, Hansen JM. Empirical H2-blocker therapy or prompt endoscopy in management of dyspepsia. Lancet 1994;343:811–16. A randomized controlled trial of 414 patients showed that those randomized to prompt EGDs were more satisfied, had lower healthcare costs, and fewer sick leave days than patients treated empirically.
Empiric antibiotic treatment of all patients without H. pylori testing is strongly discouraged. Antibiotics are of no use in non-infected patients and widespread antibiotic use may lead to resistance and adverse effects.

Treatment of active ulcers

- All four major options for treatment of active gastric and duodenal ulcers have comparable healing rates. H₂ blockers, proton pump inhibitors (PPIs), high dose antacids, and sucralfate all heal >90% of ulcers within 4–6 weeks.
- PPIs induce more rapid healing than H₂ blockers.¹⁸
- Concomitant eradication of H. pylori facilitates ulcer healing as well as decreasing recurrence.¹⁹
- Treatment is generally given for six weeks for duodenal ulcers, eight weeks for gastric ulcers.
- Persistent symptoms should prompt a search for NSAID or aspirin use, reviewing the differential diagnosis, and performing EGD. (UGI is not adequate to assess ulcer healing.)⁴
- Follow up EGD is generally indicated for gastric ulcers to assess healing and exclude the possibility of carcinoma.

Prevention of ulcer recurrence

- For most patients with PUD, by eradicating H. pylori we can now cure a previously chronic, recurrent disorder. Eradicating H. pylori infection dramatically and consistently decreases the rate of ulcer recurrence.²⁰
- This is a powerful intervention. An NIH Consensus Panel concluded that all ulcer patients with H. pylori infection require treatment with antimicrobial agents in addition to antisecretory drugs, whether on first presentation or recurrence.⁴

Which H. pylori patients should we treat?

- Definitely treat patients with:
  - duodenal ulcer
  - gastric ulcer
  - MALT lymphoma.
- Possibly treat patients with:
  - a high risk of gastric cancer
  - a gastric cancer precursor lesion
  - persistent non-ulcer dyspepsia who insist on treatment.
- Do not treat patients with:
  - no symptoms
  - GERD.

Treatment regimens for H. pylori eradication¹³

Triple regimens with the highest eradication rates:

- PPI + AC/MC: two weeks of a PPI bid, clarithromycin 500 mg bid, and amoxicillin 1 g bid (or metronidazole 500 mg bid if penicillin allergic)


- RBC + AC/MC: two weeks of ranitidine bismuth citrate 400 mg bid, clarithromycin 500 mg bid, and amoxicillin 1 gm bid (or metronidazole 500 mg bid if penicillin allergic)
- PPI + BMT: two weeks of a PPI bid, bismuth subsalicylate 2 tabs qid, metronidazole 250 mg qid, and tetracycline 250 mg qid.
- In summary, all patients with PUD who are infected with *H. pylori (>95%) should be treated with one of the above regimens. Choice of regimen depends on predicted compliance, cost, and availability.
- Consensus about the need for subsequent treatment with H₂ blockers is evolving, but at this point patients should receive the usual 6–8 week course of ulcer healing therapy following antimicrobial treatment. This is especially true for large, complicated, refractory, or gastric ulcers.
- This is a rapidly evolving field. Next year’s regimens will likely be easier to prescribe and to take without sacrificing efficacy.

**GERD**
- Treatments include PPI, H₂RA and prokinetic agents. Proton pump inhibitors are clearly superior to other agents.

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**Empirical Treatment of GERD: Odds Ratios (OR) of Outcomes for Different Agents**

<table>
<thead>
<tr>
<th>Scenario</th>
<th>OR of remitting</th>
<th>OR of improving</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₂RA v placebo</td>
<td>1.8*</td>
<td>2.6*</td>
</tr>
<tr>
<td>Prokinetic v placebo</td>
<td>1.5</td>
<td>1.7*</td>
</tr>
<tr>
<td>PPI v H₂RA</td>
<td>2.2*</td>
<td>1.7*</td>
</tr>
<tr>
<td>PPI v prokinetic</td>
<td>2.2*</td>
<td>—</td>
</tr>
</tbody>
</table>

*P < 0.05

---


**Efficacy of proton pump inhibitors versus H₂ blockers for GERD**

Patients asymptomatic after 14 days of continuous therapy:
- Ranitidine 150 mg bid 26%
- Omeprazole 10 mg qd 40%
- Omeprazole 20 mg qd 55%

Table 17.1  Agents for treatment of active peptic ulcers.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antacids</strong></td>
<td></td>
</tr>
<tr>
<td>Mg/Al hydroxide (Mylanta, Maalox)</td>
<td>2 tabs/30 ml PO qid</td>
</tr>
<tr>
<td><strong>Histamine-2 receptor antagonists</strong></td>
<td></td>
</tr>
<tr>
<td>Cimetidine (Tagamet)</td>
<td>400 mg PO bid</td>
</tr>
<tr>
<td>Ranitidine (Zantac)</td>
<td>150 mg PO bid</td>
</tr>
<tr>
<td>Famotidine (Pepcid)</td>
<td>20 mg PO bid</td>
</tr>
<tr>
<td>Nizatidine (Axid)</td>
<td>150 mg PO bid</td>
</tr>
<tr>
<td><strong>Proton pump inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Omeprazole (Prilosec)</td>
<td>10–40 mg PO qd</td>
</tr>
<tr>
<td>Lansoprazole (Prevacid)</td>
<td>15–30 mg PO qd</td>
</tr>
<tr>
<td>Pantoprazole (Protonix)</td>
<td>40 mg PO qd</td>
</tr>
<tr>
<td>Rabeprazole (Aciphex)</td>
<td>20 mg PO qd</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
</tr>
<tr>
<td>Misoprostol (Cytotec)</td>
<td>200 micrograms PO qd</td>
</tr>
<tr>
<td>Sucralfate (Carafate)</td>
<td>1 g PO qid</td>
</tr>
<tr>
<td>Ranitidine bismuth citrate (Tritec)</td>
<td>400 mg PO bid</td>
</tr>
<tr>
<td><strong>Antibiotics</strong></td>
<td></td>
</tr>
<tr>
<td>Tetracycline</td>
<td>500 mg PO qid</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>1 g PO bid</td>
</tr>
<tr>
<td>Metronidazole (Flagyl)</td>
<td>250 mg PO tid or 500 bid</td>
</tr>
<tr>
<td>Clarithromycin (Biaxin)</td>
<td>500 mg PO bid</td>
</tr>
<tr>
<td>Bismuth subsalicylate (Pepto-Bismol)</td>
<td>2 tabs PO qid</td>
</tr>
</tbody>
</table>
18 Fatigue
David Stevens

Epidemiology
Fatigue is common and often chronic
- Occasional mild fatigue is normal.
- Chronic debilitating fatigue that interferes with daily social and occupational function is not normal.
- The prevalence of chronic debilitating fatigue in primary care practice may be as high as 27%.
- The prevalence of chronic debilitating fatigue in a population based study was 18%.

Fatigue may be disabling
- Functional impairment is comparable to that seen in untreated hyperthyroidism, survivors of myocardial infarction, and survivors of sudden cardiac death.

Chronic fatigue syndrome (CFS): a small subset
- About one in seven patients with chronic disabling fatigue meet criteria for CFS.
- CFS is defined as six months of debilitating fatigue without explanation after physician evaluation plus four or more of the following symptoms for six months:
  - self reported memory or concentration impairment
  - sore throat
  - tender cervical or axillary lymph nodes
  - muscle pain, joint pain without swelling or redness
  - headaches (of a new or different type)
  - unrefreshing sleep
  - postexertional malaise lasting more than 24 hours.
- There is currently no evidence proving either a specific etiology for CFS or specific pharmacological treatment (see below).

Diagnosis
Almost anything can cause fatigue
- The differential diagnosis for chronic fatigue includes virtually all advanced organ system diseases:
  - Hypothyroidism
  - Anemia
  - Diabetes
  - HIV/AIDS
  - Malignancy
  - Drug use
  - Hepatitis
  - CHF
  - COPD
  - Sleep apnea
  - Uremia
  - Collagen vascular disease
  - Endocarditis
  - Malnutrition
  - Addison’s disease
  - Parkinson’s disease
  - Brucellosis
  - Myasthenia gravis
  - Hypokalemia
  - Tuberculosis
  - Hyponatremia
- Most of these diagnoses will be suggested by more specific symptoms (such as dyspnea, fever, or arthralgias) which often present well before the onset of fatigue.

Medical evaluation fails to elicit a cause in most patients presenting with fatigue who do not already carry a diagnosis known to cause fatigue.\(^1\)

**Laboratory investigation is usually not helpful**
- Prospective studies show no significant benefit to routine lab testing in all patients with chronic fatigue.\(^1,3\)
- Laboratory testing should be directed by findings on history and physical exam. For example, a history of intravenous drug use suggests testing for hepatitis and HIV, but not necessarily an ANA.

**Presence of occult disease**
The possibility that fatigue may be an early manifestation of a serious medical illness not elicited on blood tests has been investigated by monitoring fatigued patients prospectively over time for the development of new diagnoses. At one year of follow up, one study\(^3\) showed no significant differences in:
- new diagnoses
- diagnosed cancers
- physician visits
- hospital admissions or hospital days.
This gives more weight to the conclusion that chronic fatigue patients with otherwise normal histories and physical exams do not require extensive work ups to search for occult medical illnesses.

**Psychiatric diagnoses are common in chronic fatigue**
- Patients with chronic fatigue often have undiagnosed psychiatric illnesses.\(^1,3\)
- The prevalence of psychiatric diseases in these patients may be as high as 80%.\(^3\)

**Incidence of Anxiety and Depression in Fatigue**\(^3\)

<table>
<thead>
<tr>
<th></th>
<th>Fatigued patients (%)</th>
<th>Controls (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>58</td>
<td>12</td>
</tr>
<tr>
<td>Depression</td>
<td>56</td>
<td>0</td>
</tr>
<tr>
<td>Anxiety or depression</td>
<td>80</td>
<td>12</td>
</tr>
</tbody>
</table>

**Which came first?**
- The strong association of persistent fatigue with psychiatric illness is impressive.
- This finding, more recently validated in another study,\(^2\) prompts the question “Is persistent fatigue the cause or effect of depression or anxiety?”. A study of patients presenting with fatigue who were then diagnosed with psychiatric disorders\(^2\) found that...
  1. in 56% of patients, the psychiatric disorder predated the fatigue by at least one year.
  2. in 35% of patients, the fatigue and psychiatric illness began at about the same time.

Comparison of 102 Fatigued Patients with 26 Non-fatigued Controls\(^3\)
(numbers represent mean values)

<table>
<thead>
<tr>
<th>Test</th>
<th>Patients (N = 102)</th>
<th>Controls (N = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hct (%)</td>
<td>41.9</td>
<td>42.0</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>117</td>
<td>103</td>
</tr>
<tr>
<td>T4 (nmol/l)</td>
<td>113.3</td>
<td>110.7</td>
</tr>
<tr>
<td>T3 (nmol/l)</td>
<td>2.2</td>
<td>2.1</td>
</tr>
<tr>
<td>TSH (mU/l)</td>
<td>2.0</td>
<td>1.9</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>K(^+) (meq/l)</td>
<td>4.5</td>
<td>4.4</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>20.5</td>
<td>9.6</td>
</tr>
<tr>
<td>CXR (% abnormal)</td>
<td>25.2</td>
<td>27.3</td>
</tr>
</tbody>
</table>

This was a prospective study performed on patients in a general medical practice (not a referred population). The only lab test with a significant difference between the two groups was the ESR (P = .01). The clinical significance of this finding is not clear.

5 Lane TJ, Manu P, Matthews DA. Depression and somatization in the chronic fatigue syndrome. Am J Med 1991;91:335–44. Depression was measured by the Beck Depression Inventory and anxiety was measured by the Modified Somatic Perception Questionnaire.
3. only 10% of patients had fatigue more than three months before their psychiatric illness began. While these findings do not prove etiology, they strongly suggest that the psychiatric disorder is a primary diagnosis and not simply a result of fatigue. This conclusion is further supported by a study demonstrating that patients with rheumatoid arthritis, a chronic and debilitating disease, have a much lower prevalence of psychiatric disease than those with chronic fatigue.6

Etiology of chronic fatigue syndrome

- Many researchers have proposed that CFS has a specific etiology that distinguishes it from chronic fatigue without the associated signs and symptoms stated above.
- Epstein-Barr virus infection, once suspected of being the etiologic agent of CFS, has been shown to be no more active in people with CFS than in those without it.7
- CFS is similar to chronic fatigue not meeting CFS criteria in its high association with psychiatric disorders and the high proportion in which the psychiatric disorder predates the fatigue.6

Prognosis

- Most patients with unexplainable chronic fatigue remain fatigued on follow up.
- In one study at one year of follow up, fatigue improved in only 28% of patients.3
- So, while fatigue of unclear etiology may not portend a serious illness, it also does not often spontaneously remit.

Treatment

Medications

- Many studies have assessed potential treatments ranging from antihistamines8 to antidepressants9 to vasoactive medications.
- None of these trials have shown a benefit from treatment.

Corticosteroid therapy

- Chronic fatigue syndrome has been associated with mild hypocortisolism. Some investigators have postulated a benefit with oral steroid therapy.
- In a recent study, 32 patients with fatigue in the absence of any psychiatric disorder (a very small subset of 218 fatigued patients who were screened) were randomized to low dose (5–10 mg qd) hydrocortisone versus placebo.10
- A modest advantage was noted in treated patients in four of five disability scores.

Exercise therapy

- In 1996, the Joint Working Group of the Royal Colleges of Physicians, Psychiatrists, and General Practitioners recommended graded exercise and antidepressants for patients with chronic fatigue syndrome.11

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10 Cleare AJ, Heap E, Malhi GS et al. Low-dose hydrocortisone in chronic fatigue syndrome: a randomised crossover trial. Lancet 1999;353:453–8. All patients received both treatments (for one month each) in blinded fashion in random order. Disability scores were reduced by 0.6–1.1 units on eight unit scales (P < 0.05).

In a trial of a graded aerobic exercise program, 66 patients with CFS who had no psychiatric disorder were randomized to aerobic exercise (treatment) versus flexibility exercises (control). After 12 weeks, 51% of treated patients felt significantly improved compared to 27% of controls. The total fatigue score was significantly better in the treatment group.

In a more recent trial, 136 patients with chronic fatigue syndrome were randomized to graded exercise 3–5 times per week, fluoxetine (20 mg qd), both, or neither. At six months, patients randomized to exercise had modestly improved work capacity and less fatigue, but patients randomized to fluoxetine showed no improvement in these variables.

Cognitive therapy

The most impressive increases in functional status reported in studies of fatigued patients have employed cognitive behavioral therapy, an approach based on the theory that “inaccurate and unhelpful beliefs, ineffective coping behavior, negative mood states, social problems, and pathophysiological processes all interact to perpetuate the illness”.

According to theory, a person’s belief that he or she will fail in a certain activity may lead to loss of energy in initiating that activity. Similarly, a belief that CFS is necessarily debilitating may lead to a decreased effort to try to overcome it, thereby perpetuating the fatigue.

Sixty patients consecutively referred to an infectious disease clinic who met the CFS definition by the Oxford criteria were randomized to standard medical care or cognitive behavior therapy plus standard medical care. The results were as follows.

<table>
<thead>
<tr>
<th>Cognitive Therapy in the Treatment of CFS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Results</td>
<td></td>
</tr>
<tr>
<td>Achieved normal function</td>
<td>73%</td>
</tr>
<tr>
<td>Significantly improved function</td>
<td>73%</td>
</tr>
</tbody>
</table>

Additional findings

- Patients receiving cognitive behavioral therapy were far less likely to report that they were avoiding exercise.
- Patients receiving cognitive therapy were also less convinced that their illness was mainly physical or that it was caused by a virus.
- This study was reinforced by another trial of 60 patients which demonstrated similar outcomes.

Cognitive therapy: study conclusions

- Patients’ beliefs about their illnesses affect their outcome. Avoidance of exercise and emphasis on the physical nature of their condition were decreased.


14 Sharpe M, Hawton K, Simkin S et al. Cognitive behaviour therapy for the chronic fatigue syndrome: a randomised controlled trial. BMJ 1996;312:22–6. Significant functional improvement occurred in 72% of patients treated with cognitive therapy compared with 28% of those treated with standard medical therapy. Results were sustained for one year after discontinuation of therapy.

The main concerns about putting this study into practice are:

- therapy was administered by psychiatrists or psychologists
- therapy consisted of 16 one-hour sessions over four months
- patients were selected from a subspecialty referral center.

15 Deale A, Chalder T, Marks I, Wessely S. Cognitive behavior therapy for chronic fatigue syndrome: a randomized controlled trial. Am J Psych 1997;154(3):408–14. At final follow up, 70% of the completers in the cognitive behavior therapy group achieved good outcomes (substantial improvement in physical functioning) compared with 19% of those in the relaxation group who completed treatment.
of the illness and its possible viral etiology are associated with a worse prognosis.

- A collaborative approach with the patient emphasizing re-evaluating illness beliefs and behavior may lead to significant improvement in function.
- Patients with unexplained chronic fatigue should be considered for referral for cognitive behavior therapy.

Summary of principles in management of chronic fatigue

- Fatigue is a common and often serious problem.
- The differential diagnosis is very long and does not lend itself to a universal approach.
- Comprehensive laboratory investigation is usually not helpful.
- Chronic fatigue syndrome represents a small subset of all patients with fatigue.
- There is no evidence to suggest that patients with chronic fatigue syndrome should be treated differently from other patients with fatigue.
- Medical therapy is of little or no benefit in the treatment of chronic fatigue.
- Cognitive therapy has been shown to substantially improve symptoms and function in patients with chronic fatigue.
- Cognitive therapy should be provided by a trained specialist.
Headache
Douglas Bails and Danielle Ofri

Epidemiology
Incidence
• Headache is believed to be the most common pain experienced by humans.
• There were more than 12.7 million office visits for headache in 1997.¹
• Migraine² and tension³ headaches are responsible for a significant amount of absenteeism and lost productivity.

Diagnosis
History
Overview
• Typically, the physical exam and other diagnostic studies are entirely normal. Therefore, headaches are classified by history.
• For an acute headache, the most pressing issue is to rule out subarachnoid hemorrhage, subdural hematoma, and meningitis.
• For a chronic headache, the following characteristics are helpful.⁴

Temporal pattern of pain
• Tension: lasts hours to days, predominantly in the evening
• Migraine: lasts hours, often awakens the patient from sleep
• Cluster: occurs at the same time daily for minutes to hours
• Tumor: awakens the patient from sleep
• Subarachnoid hemorrhage: precipitated by exertion

Character and location of pain
• Tension: diffuse, steady, band-like
• Migraine and cluster: throbbing, unilateral, retro-orbital

Alleviating and exacerbating factors
• Tension: relieved by relaxation, massage; worsened by eye strain and emotional tension
• Migraine: helped by sleep, vomiting; exacerbated by exertion, menses, hunger, lack of sleep
• Cluster: nothing helps; worsened by high altitude, hunger, exertion

Associated symptoms
• Migraine:
  — prodrome: 24–48 hours of non-specific symptoms (fatigue, depression, food craving, hyperactivity)
  — aura: transient focal neurologic symptoms (visual, sensory, motor) that precede headache by 1–2 hours and resolve within 60 minutes
  — nausea, vomiting, phonophobia, and photophobia during the headache.

³ Schwartz BS, Stewart WF, Simon D, Lipton RB. Epidemiology of tension-type headache. JAMA 1998;279:381–3. 13,345 people were contacted by telephone survey; more than 5000 reported experiencing tension headaches in the past year. Of those, 8% reported lost workdays because of their headaches, while 44% reported decreased effectiveness at work, home, or school.
⁴ Smetana GW. The diagnostic value of historical features in primary headache syndromes. Arch Intern Med 2000;160:2729–37. In this meta-analysis, the following symptoms were most predictive of migraine compared with tension headache.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Likelihood ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>19</td>
</tr>
<tr>
<td>Photophobia</td>
<td>6</td>
</tr>
<tr>
<td>Phonophobia</td>
<td>5</td>
</tr>
<tr>
<td>Food triggers</td>
<td>4</td>
</tr>
<tr>
<td>Exacerbation by activity</td>
<td>4</td>
</tr>
</tbody>
</table>
• Cluster: ipsilateral flushing and eye tearing
• There is no prodrome in tension headache, tumor, or subarachnoid hemorrhage.

Age of onset
• Tension: typically begins in adulthood
• Migraine: begins in adolescence
• Cluster: typically occurs at ages 20–60 in distinct clusters

Family history
• Migraine: 40% of patients have a positive family history
• Cluster, tension: no clear familial transmission

Physical exam
• Vital signs: tachycardia (suggested infection), hypertension
• Fundi and pupils: papilledema (necessitates CT)
• Meningeal signs, neurologic abnormalities
• Palpation for focal pathology: temporomandibular joint, sinuses, temporal arteries
• Unilateral tearing and conjunctival injection (suggesting cluster)

Other diagnostic tests
Blood tests
• Complete blood count and erythrocyte sedimentation rate (rarely helpful)

Imaging
• Imaging studies\(^5\) and electroencephalogram\(^6\) are unlikely to reveal significant abnormalities in patients with normal neurological exams and who fit the clinical criteria for migraine, tension, or cluster headache.
• While serious intracranial disease is only present in <1% of headache patients, the consequences of missing the diagnosis are severe.
• Virtually all significant tumors and bleeds can be seen on non-contrast CT scan.
• Contrast dye is indicated if the patient is HIV positive or if cerebral metastases or vascular malformation are suspected.
• If a bleed is in the differential diagnosis, CT is preferable to MRI.

Indications for lumbar puncture
• Meningeal signs
• Fever in the setting of nuchal rigidity or photophobia
• Suspicion of subarachnoid hemorrhage after normal CT or MRI

Danger signs suggesting serious intracranial disease
• Extraordinary severity: “the worst headache of my life”\(^7\)
• Onset of headache with exertion is characteristic of subarachnoid hemorrhage (as opposed to the exacerbation by exertion seen with migraines).

Peter Fallow’s headache
The telephone blasted Peter Fallow awake inside an egg with the shell peeled away and only the membranous sac holding it intact. Ah! The membranous sac was his head, and the right side of his head was on the pillow, and the yolk was as heavy as mercury, and it rolled like mercury, and it was pressing down on his right temple and his right eye and his right ear. If he tried to get up to answer the telephone, the yolk, the mercury, the poisoned mass, would shift and roll and rupture the sac, and his brains would fall out.

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\(^7\) Morgenstern LB, Luna-Gonzales H, Huber JC Jr et al. Worst headache and subarachnoid hemorrhage: prospective, modern computed tomography and spinal fluid analysis. Ann Emerg Med 1998;32:297–304. Of 107 patients with the worst headache of their lives, SAH was diagnosed in 18 by CT and in two more by CSF analysis (of those who had normal CT exams).
- Progressively worsening headache or change in normal pattern of headache
- Abnormal vital signs
- Decreased alertness or cognition
- Focal neurologic exam
- Trauma in the past three months suggests subdural hematoma.

**Tension headache**
- The most common cause of headache
- Probably a heterogeneous group of disorders. The leading theory postulates cranial muscle contraction leading to inflammation and pain. Many investigators support an etiology similar to migraine.

**Clinical presentation**
- Tension headache typically presents as a constant, bilateral, throbbing pain in the "hat band" distribution.
- The most common precipitating factors are stress, depressed mood, and lack of sleep.
- Important factors in diagnosing tension headache are the absence of nausea, vomiting, and photophobia; however, any severe pain can cause vomiting.

**Treatment**
- Identify and treat inciting factors: excess stress, eye strain, and depression.
- Over the counter analgesic preparations (aspirin, acetaminophen, ibuprofen, naproxen)
- Advance to prescription NSAIDs (indomethacin, sulindac)
- Advance to combination analgesic medications. These usually contain acetaminophen or aspirin in combination with caffeine. Combination drugs with sedatives have little data to support their efficacy.
- In some cases, prophylaxis with tricyclic antidepressants or anticonvulsant medications may be beneficial for chronic tension headache.

**Cluster headache**
- The typical patient is a thin male smoker, 20–50 years old.
- The incidence is about one fifth that of migraine.
- No evidence for familial transmission.
- Circadian rhythm of pain: the patient can “set his watch” to the symptoms.
- Short-lived, severe, unilateral and retro-orbital pain awakening the patient. The patient cannot lie still (the opposite of migraine).
- Associated symptoms include ipsilateral lacrimation, rhinorrhea, and conjunctival injection.
- Appearance in distinct clusters, typically lasting 4–6 weeks, with a disease free period of between three months and five years.

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Exacerbation by severe emotional distress, ethanol, high altitude, or medications such as vasodilators or nitrates.

Treatment of these brief but severe headaches can be difficult. There is some evidence that zolmitriptan\textsuperscript{11} and sumatriptan\textsuperscript{12} are beneficial.

Verapamil may be helpful in prevention.\textsuperscript{13}

**Migraine headache**

- Four to twelve percent of the population is affected, with a 4:1 female predominance.\textsuperscript{14}
- Usually begins in childhood or adolescence.
- Strong family predilection
- Often divided into two categories:
  - migraine with aura (classic migraine) occurs in one third of patients
  - migraine without aura (common migraine) occurs in the majority of patients. Many experience both types.

**Etiology\textsuperscript{15}**

- A “spreading depression” of neural activity may lead to secondary perfusion changes which activate the trigeminal nerve. This is the likely cause of the headache pain.
- Pain signals travel to higher centers via serotonin mediated pathways.
- Nitric oxide may play a role as well.

**Clinical presentation**

- May be preceded by a prodrome or a neurological aura. Auras are almost always visual and can be accompanied by sensory, aphasic, auditory, or motor symptoms.
- Common triggers include wine, cheese, nuts, chocolate, odors, fatigue, bright lights, loud sounds, menses, alcohol, and tension.
- Medications that may exacerbate migraine headaches include nitrates, vasodilators, and contraceptives.
- Pain typically begins as a unilateral, pulsating or throbbing headache, often frontotemporal or retro-orbital, which becomes generalized.
- Associated with nausea, vomiting, photophobia, or phonophobia.
- Aggravated by routine physical exertion. Most patients prefer to lie still in a dark room or sleep.
- Typically lasts hours at a time; often begins upon waking.

**General principles of treatment**

- Headache diaries help patients identify headache patterns, triggers, and response to medications.
- Removal of triggers is a logical first step, but most patients do not find significant relief.
- Prompt treatment of acute migraine in its earliest phase is the key to effective therapy. Many patients find they have


\textsuperscript{14} Stewart WF, Lipton RB, Celentano DD, Reed ML. Prevalence of migraine headache in the United States: relation to age, income, race, and other sociodemographic factors. JAMA 1992; 267:64–9. This community-based survey of 20000 people found that disability from migraines was inversely related to headache frequency.


A complicated migraine is one which leaves a permanent neurologic deficit. A hemiplegic migraine is associated with unilateral paralysis which may outlast the headache.
a window of opportunity for treatment, after which medications seem to work less well.

- Oral absorption may be impaired, even when patients do not experience nausea or vomiting.
- Sleep or rest in a dark room can be helpful.
- Consider prophylaxis for patients with frequent headaches (see below).
- Engage the patient in a plan for treatment that includes:
  - availability of medication for immediate use
  - low and high potency medications for mild and severe attacks
  - adjunctive antiemetics
  - non-oral administration when there is nausea or vomiting
  - rescue medications if the first medication does not work.

**Acute treatment of mild to moderate migraine**

- Common analgesic preparations (aspirin, acetaminophen, ibuprofen, naproxen\(^\text{16}\)) and prescription NSAIDS\(^\text{17}\)
- Combination preparations: aspirin, acetaminophen, and caffeine (Excedrin-ES)\(^\text{18}\)
- There is some concern that caffeine can lead to rebound headaches.
- Antiemetics (prochlorperazine, chlorpromazine, and metoclopramide) should be available for migraines of all severity levels, since nausea and vomiting can sometimes be more bothersome than the actual headache pain. Antiemetics alone may be sufficient to treat the entire episode.\(^\text{19}\)
- For moderate to severe migraines consider the following.

**Ergot preparations**

- Used for decades, but there are few data from randomized controlled trials.\(^\text{20}\)
- Available in various routes of administration (oral, sublingual, suppository), usually in combination preparations. All contain 1–2 mg of ergotamine.
- Nausea and vomiting are common side effects and may require antiemetics.
- Can also cause vasoconstriction, abdominal pain, diarrhea.
- Contraindicated in coronary artery disease, peripheral vascular disease, severe hypertension, chronic liver disease.
- Chronic use can lead to dependence, analgesic headache, and “ergotism” (vasoconstriction, muscle pain, rash).

**Butalbital**

- Like ergots, the barbiturate drug butalbital has been used traditionally, but there are almost no well conducted trials supporting its efficacy.
- Usually part of combination preparation (Fioricet, Fiorinal).
- Concerns about dependence, withdrawal and medication overuse headache limit its use.

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\(^{16}\) Treves TA, Streiffler M, Korczyn AD. Naproxen sodium versus ergotamine tartrate in the treatment of acute migraine attacks. Headache 1992;32: 280–2. In a double blind study of 79 patients with mild migraine, naproxen and ergotamine were equally effective.


\(^{18}\) Lipton RB, Stewart WF, Ryan RE Jr et al. Efficacy and safety of acetaminophen, aspirin, and caffeine in alleviating migraine headache pain. Three double-blind, randomized, placebo-controlled trials. Arch Neurol 1998;55:210–17. 1357 patients were randomized to Excedrin or placebo. Within two hours, pain was reduced to mild or none in 59% in the treatment group vs 33% in the controls. There was also improvement in nausea, photophobia, phonophobia, and disability scores.


**Lidocaine**
- Intranasal lidocaine drops are fast acting and can be effective, but relapses are common.  

**Opiates**
- Effective pain relievers, but are associated with dependence and withdrawal.
- Butorphanol tartrate (Stadol) nasal spray provides more rapid onset of action than oral opiate preparations.

**Dihydroergotamine (DHE)**
- An ergotamine derivative that is available for parenteral or intranasal use.
- A much weaker vasoconstrictor than traditional ergotamine, with fewer side effects and less rebound headache. There is more evidence to support its use.
- Contraindicated in pregnancy, lactation, uncontrolled hypertension, peripheral vascular disease, and coronary artery disease.

**Triptans**
- Serotonin agonists are effective at aborting migraines, without the complications of psychoactive impairment or dependence. They also offer the advantage of relieving associated nausea and vomiting without necessarily requiring an additional antiemetic. Triptans are substantially more expensive than older medications.
- Beyond relief of headache, sumatriptan has also been demonstrated to reduce productivity loss in the workplace.
- Triptans have not necessarily been proven more effective than traditional therapies such as DHE or NSAIDS with antiemetic medications.
- The various triptans differ in pharmacokinetics and there are few head to head trials comparing them: sumatriptan, zolmitriptan, naratriptan, and rizatriptan. (See references 28, 29, 30.)
- Sumatriptan, approved by the FDA in 1992, is the most widely researched triptan and the only one available in non-oral forms. The subcutaneous route appears to be more effective than the oral or intranasal route, but has more adverse effects.
- Because of its potential to cause coronary artery vasospasm, sumatriptan is contraindicated in patients with ischemic heart disease. Serious coronary events have been associated with sumatriptan, but are extremely rare.
- Intranasal sumatriptan often leaves a bitter taste and nausea, but may be an alternative for patients who:
  - need a more rapidly acting treatment than oral medication
  - are vomiting
  - are not comfortable with injectable medications.

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24 Winner P, Ricalde O, Le Force B, Saper J, Margul B. A double-blind study of subcutaneous dihydroergotamine vs subcutaneous sumatriptan in the treatment of acute migraine. Arch Neurol 1996;53:180–4. 295 patients were randomized to sumatriptan or DHE. There was no difference in the number of subjects who found relief at four hours (85%), but there were more recurrences at 24 hours with sumatriptan (45%) as compared to DHE (18%).

25 Tfelt-Hansen P, Henry P, Mulder LJ et al. The effectiveness of combined oral lysine acetylsalicylate and metoclopramide compared with oral sumatriptan for migraine. Lancet 1995;346: 923–6. In this RCT of 421 patients, a salicylate (equivalent to 900 mg aspirin) plus metoclopramide was as effective as oral sumatriptan.


• Side effects include flushing, tingling sensations, hypertension, fatigue, and chest discomfort. Actual vasoconstrictive events are rare, but sumatriptan is contraindicated in patients with a history of ischemic disease, uncontrolled hypertension, or Prinzmetal angina.
• All triptans in oral forms appear to be as effective as oral sumatriptan.28
• One trial showed rizatriptan to be slightly more effective than naratriptan.29
• The triptans are probably safe for repeated use in recurrent headaches.30

Migraine prophylaxis
• Indicated in patients with two or more attacks per week or in those with a significant disruption of daily life. Most prophylactic medications offer about a 50% improvement over placebo, usually in terms of frequency of headache rather than severity of headache. There are few head to head studies of different agents.31
• As efficacy does not appear to vary significantly, the choice of agent depends upon side effect profile, patient comorbidity, and individual success rates.
• Medication failure usually occurs because of inadequate dosing or unwillingness to wait the 2–3 months necessary for effective prophylaxis.
• The most commonly used prophylactic agents are β blockers,32 tricyclic antidepressants,33 anticonvulsant medications, and calcium channel blockers.34
• High dose riboflavin has been shown to reduce the frequency of headaches with minimal side effects.35
• Aspirin36 and NSAIDS37 may also be beneficial.
• Methysergide is limited to severe refractory cases because of the risk of retroperitoneal and pleural fibrosis.
• There are several randomized controlled trials supporting non-pharmacological therapy (biofeedback, relaxation, breathing exercises, and directed imagery). Efficacy can be as high as with pharmacological therapy.

Other headache syndromes
Subdural hematoma
• Mild, steady, unilateral headache occurring days to weeks after trauma. There is a crescendo pattern, progressing from headache to sensorium change to stupor to coma.

Subarachnoid hemorrhage (SAH)
• Sudden, acute headache which localizes to the occiput and neck, often precipitated by exertion. Migraines and tension headaches can be worsened by exertion, but they are not precipitated by exertion.

28 Goadsby PJ, Ferrari MD, Olesen J et al. Eletriptan in acute migraine: a double-blind, placebo-controlled comparison to sumatriptan. Neurology 2000; 54:156–63. 857 patients were randomized to placebo, sumatriptan (100 mg) or eletriptan (20, 40, or 80 mg). At two hours, the percentage of patients with mild or no pain in the five groups were 24%, 55%, 54%, 65% and 77%, respectively.
29 Bomhof M, Paz J, Legg N et al. Comparison of rizatriptan 10 mg vs naratriptan 2.5 mg in migraine. Eur Neurol 1999;42:173–9. 522 patients were randomized to rizatriptan or naratriptan. At two hours, 44% of the rizatriptan group were pain free v 27% on naratriptan.
35 Schoenen J, Jacqy J, Lenaerts M. Effectiveness of high-dose riboflavin in migraine prophylaxis: a randomized controlled T trial. T Neurology 1998; 50:466–70.
There may be a severe warning or sentinel headache days to weeks prior. This “thunderclap” headache rapidly intensifies over seconds to minutes, then can linger for days to weeks.

SAH is caused by a ruptured congenital aneurysm, hematologic disease, or inflammation.

SAH misdiagnosis is a source of significant morbidity and mortality.\textsuperscript{39}

Confounding issues that can lead to misdiagnosis:\textsuperscript{40}

- SAH can spontaneously improve before worsening (rebleeding).
- Classic signs are often not present.
- Comorbid presentations (head injury after syncope, hypertension, EKG abnormalities) can dominate the clinical evaluation.
- CT scan loses sensitivity as time from onset of SAH increases.
- CT can be falsely negative when the patient’s hematocrit is $<30$.
- Xanthochromia (yellow cerebrospinal fluid) may be absent in the first 12 hours after bleeding or after two weeks.

Meningitis

- Presents as an intense, throbbing, global headache due to inflammation of the meninges. Common etiologies include infection (bacterial, viral) and malignancy. The headache can progress rapidly or gradually.
- Associated findings include nuchal rigidity, photophobia, fever, seizures, lethargy and focal deficits.
- Diagnosis is by lumbar puncture; treatment depends on the etiology.

Temporal (giant cell) arteritis

- Typically presents in older patients as unilateral or bilateral burning scalp pain in the temporal region.
- Associated findings include temporal artery tenderness and nodularity, jaw and tongue claudication, malaise, weight loss, fever, sweats, anemia, and elevated erythrocyte sedimentation rate.
- There is a high association with polymyalgia rheumatica: stiff, painful trunk muscles.
- Untreated temporal arteritis can lead to ischemic optic neuritis and permanent loss of vision.
- Diagnosis is by history and temporal artery biopsy.
- Treatment is with high dose glucocorticoids. Addition of methotrexate may reduce relapse and the cumulative glucocorticoid dose.\textsuperscript{41}

Intracranial mass

- A non-specific headache syndrome
- Some clues to the diagnosis include an intermittent, deep, dull aching which is exacerbated by stooping, coughing, sudden head movement, or exertion.


\textsuperscript{39} Mayer PL, Awad IA, Todor R et al. Misdiagnosis of symptomatic cerebral aneurysm: prevalence and correlation with outcome at four institutions. Stroke 1996;27:1538–63. In a retrospective analysis of 217 patients with SAH, 54 were initially misdiagnosed. These patients were more likely to have presented in good clinical condition and more likely to have poor outcomes than those who were initially correctly diagnosed.


Signs suggesting meningitis

Kernig sign: with the supine patient’s hips and knees flexed 90°, complete flexion of the hips elicits neck pain.

Brudzinsky (“nap of the neck”) sign: the doctor flexes the neck of the supine patient; a flexion response in the lower extremities suggests meningitis.

This headache can interfere with sleep.
Elevated intracranial pressure can cause nausea, vomiting, and focal deficits.

**Pseudotumor cerebri headache**
- Similar to those of intracranial mass
- Patients tend to be young, female, and obese.
- Papilledema is usually present and often severe.
- CT scan usually shows normal sized ventricles.
- There can be visual abnormalities, particularly visual field deficits.

**Hypertensive headache**
- Generally seen only with diastolic pressures over 120 mmHg.
- There is usually a mild throbbing in the occipital region.

**Sinus headache**
- Is described as a painful fullness that is worse in the morning and when bending over.

**Temporomandibular joint syndrome**
- Is associated with headache in the parietal region that is precipitated by chewing.

**Rebound headaches**
- Medication overuse headache is most often seen with chronic use of ergotamine, caffeine, and combination medications in migraine, but can happen with any analgesic. This should be suspected if patients report daily headaches despite increasing doses of medications.
- Rebound headache occurs when analgesics are abruptly withdrawn. Ergotamine, caffeine, narcotics, and opiates are the most common offenders, as well as NSAIDs and APAP.
- Treatment can be difficult, as patients are often reluctant to discontinue their medications. Addition of a prophylactic agent can aid in tapering the offending analgesic.

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<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage form</th>
<th>Usual dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>81/325 mg</td>
<td>650 mg PO q4–6 h</td>
</tr>
<tr>
<td>Acetaminophen (Tylenol)</td>
<td>325/500 mg</td>
<td>1000 mg PO q4–6 h</td>
</tr>
<tr>
<td>Ibuprofen (Motrin, Advil)</td>
<td>400/600 mg</td>
<td>400–600 mg PO q6 h</td>
</tr>
<tr>
<td>Naproxen (Anaprox, Aleve)</td>
<td>200/275/550 mg</td>
<td>275 mg q6–8 h, 550 mg PO bid</td>
</tr>
<tr>
<td>Aspirin/acetaminophen/caffeine</td>
<td></td>
<td>1–2 tabs PO q6 h</td>
</tr>
<tr>
<td>(Excedrin-ES or Migraine)</td>
<td></td>
<td>Tension HA: 1–2 tabs q4 h</td>
</tr>
<tr>
<td>Isometheptene/dichloralphenazone/</td>
<td></td>
<td>Migraine HA: 2 tabs q1 h; max: 5 in 12 h</td>
</tr>
<tr>
<td>acetaminophen (Midrin)</td>
<td></td>
<td>1–2 tabs PO q 4–6 h, max: 6 per day</td>
</tr>
<tr>
<td>Butalbital/aspirin/caffeine (Fiorinal) ± codeine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Butalbital/acetaminophen/caffeine (Fioricet) ± codeine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ergotamine (Ergostat)</td>
<td>2 mg tabs</td>
<td>1 tab sublingual at onset, then 1 q30 min; max: 3 per day, 5 per wk</td>
</tr>
<tr>
<td>Ergotamine/caffeine (Cafergot)</td>
<td>1 mg tabs</td>
<td>2 tabs PO at onset, then 1 PO q30 min × 4, max: 6 per day, 10 per wk</td>
</tr>
<tr>
<td></td>
<td>2 mg suppositories</td>
<td>1 PR at onset; may repeat at 1 h, max: 2 per day, 5 per wk</td>
</tr>
<tr>
<td>Dihydroergotamine (DHE 45)</td>
<td>1 mg/ml</td>
<td>0.5–1 ml IM at onset, then q1 h, max: 3 ml per day, 6 ml per wk</td>
</tr>
<tr>
<td>Dihydroergotamine (Migranal)</td>
<td>4 mg/ml nasal spray</td>
<td>0.5 mg spray in each nostril q15 min, max: 3 mg per day, 4 mg per wk</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>4% aqueous solution</td>
<td>0.5 ml to ipsilateral nostril over 30 seconds, can be repeated after 2 min</td>
</tr>
<tr>
<td>Sumatriptan (Imitrex)</td>
<td>6 mg vial</td>
<td>6 mg SQ at onset; may repeat at 2 h; max: 12 mg per day</td>
</tr>
<tr>
<td></td>
<td>25/50 mg tabs</td>
<td>25–100 mg PO at onset, may repeat at 2 h; max: 200 mg per day</td>
</tr>
<tr>
<td></td>
<td>5/20 mg nasal spray</td>
<td>5–20 mg spray in one nostril; may repeat at 2 h, max 40 mg/day</td>
</tr>
<tr>
<td>Naratriptan (Amerge )</td>
<td>1/2.5 mg tabs</td>
<td>1 or 2.5 mg PO at onset; may repeat dose at 4 h; max: 5 mg per day</td>
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<tr>
<td>Zolmitriptan (Zomig)</td>
<td>2.5/5 mg tabs</td>
<td>1.25–5 mg at onset; may repeat at 2 h; max: 10 mg per day</td>
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<tr>
<td>Rizatriptan (Maxalt)</td>
<td>5/10 mg tabs</td>
<td>5–10 mg at onset, may repeat at 2 h; max: 30 mg per day</td>
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<tr>
<td>Propranolol (Inderal)</td>
<td>10/20/80 mg</td>
<td>407–120 mg PO q12 h</td>
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<tr>
<td>Timolol (Blocadren)</td>
<td>5/10/25 mg</td>
<td>10–15 mg PO bid</td>
</tr>
<tr>
<td>Divalproex (Depakote)</td>
<td>125/250/500 mg</td>
<td>250–500 mg PO bid</td>
</tr>
<tr>
<td>Amitriptyline (Elavil)</td>
<td>10/25/50/75/ 100/150 mg tabs</td>
<td>10–150 mg PO per day</td>
</tr>
<tr>
<td>Verapamil (regular or slow release)</td>
<td>Many preparations</td>
<td>240–480 mg PO per day</td>
</tr>
</tbody>
</table>
Heart failure is present when an abnormality of cardiac function is responsible for the inability of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues and/or can do so only from an abnormally elevated ventricular diastolic volume.\(^1\)

**Epidemiology**

**Prevalence**
- Heart failure affects 4.6 million Americans and accounts for 45,000 deaths a year.\(^2\)
- Deaths and hospital discharges for heart failure more than doubled between 1980 and 2000. The increasing prevalence is due to the aging of the population and to improved survival of patients after myocardial infarction (MI).
- In 75% of cases, heart failure is preceded by hypertension.
- Heart failure is the most common cause of hospitalization in people over 65.

**Prevalence (%) of Heart Failure by Age and Sex**

<table>
<thead>
<tr>
<th>Age</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–29</td>
<td>0.3</td>
<td>0.1</td>
</tr>
<tr>
<td>30–39</td>
<td>0.2</td>
<td>0.4</td>
</tr>
<tr>
<td>40–49</td>
<td>1.6</td>
<td>0.6</td>
</tr>
<tr>
<td>50–59</td>
<td>4.7</td>
<td>2.1</td>
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<tr>
<td>60–69</td>
<td>6.3</td>
<td>4.7</td>
</tr>
<tr>
<td>70–79</td>
<td>9.8</td>
<td>8.8</td>
</tr>
<tr>
<td>≥80</td>
<td>11.1</td>
<td>11.2</td>
</tr>
</tbody>
</table>

**Etiology**
The most common causes of heart failure are now thought to be:
- coronary artery disease
- idiopathic dilated cardiomyopathy
- hypertension/left ventricular hypertrophy
- valvular heart disease
- toxins: alcohol, doxorubicin (Adriamycin), cocaine, heroin
- infiltrative disease: amyloidosis, hemochromatosis, sarcoidosis.

**Diagnosis**

**Overview**
- Distinguish between systolic and diastolic dysfunction.
- If systolic dysfunction is present, distinguish between ischemic and non-ischemic heart failure. Is coronary artery disease present? Has the patient ever undergone coronary angiography? Idiopathic dilated cardiomyopathy is a diagnosis of exclusion.
- Is diastolic dysfunction present? If so, does the patient have hypertension or another underlying cause (for example, amyloidosis)?

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In heart failure, it is imperative to know the condition of the coronary arteries. In coronary artery disease, it is crucial to know the condition of the left ventricle.
HEART FAILURE

History
- Dyspnea on exertion, paroxysmal nocturnal dyspnea, sleeping on extra pillows to avoid lying flat, lower extremity swelling.

Physical exam: systolic dysfunction (ejection fraction <0.40)³
- **Very helpful**: abnormal apical impulse (displaced laterally and downward, and sustained)
- **Somewhat helpful**: tachycardia, hypotension, pulse pressure <33% of systolic pressure, third heart sound, rales
- **Helpful only when present** (**specific, not sensitive**): jugular venous distention, edema

Basic diagnostic tests
- **Blood tests**: complete blood count, electrolytes, liver function tests, thyroid function tests
- **Urinalysis**: for glomerular disease
- **Electrocardiogram**: for evidence of atrial fibrillation, previous MI, left ventricular hypertrophy (LVH), bundle branch block, or left axis deviation. By these criteria, the sensitivity of ECG for systolic dysfunction is 94%, specificity 61%.⁴ Since 94% of patients with heart failure have one of these five abnormalities, a normal ECG is reassuring (LR = 0.10).
- **Chest radiograph**: cardiomegaly was 51% sensitive and 79% specific in diagnosing reduced ejection fraction.⁵

Additional diagnostic tests
- **Echocardiogram** assesses systolic function, left ventricular wall thickness, valvular disease, indices of diastolic function, and ventricular thrombi. It is the most useful tool in the evaluation of heart failure.
- **Radionuclide ventriculogram** measures ejection fraction; it provides little other information. Also known as a gated pool or multiple gated acquisition (MUGA) scan.
- **Cardiac catheterization** accurately assesses LV function.
- **Exercise stress testing** should be considered in all patients with heart failure. It assesses workload capacity and possible concurrent coronary artery disease.
- **Holter monitoring** to screen for arrhythmias is not routinely indicated in patients with heart failure. However, an assessment of risk of sudden death may be appropriate in patients with severe left ventricular dysfunction. Moreover, a complaint of syncope or presyncope must be taken very seriously in a patient with heart failure.
- Useful markers for sudden death include non-sustained ventricular tachycardia on Holter monitoring or a positive signal averaged ECG. Presence of high risk markers should prompt referral to a cardiologist.

Proportional pulse pressure:
- **Systolic BP** – **diastolic BP**

<table>
<thead>
<tr>
<th>Systolic BP</th>
<th>Proportional pulse pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP</td>
<td></td>
</tr>
</tbody>
</table>


Segmental hypokinesis suggests myocardial ischemia as the etiology; **global** hypokinesis suggests idiopathic dilated cardiomyopathy.

Causes of high output failure
- Hyperthyroidism
- Severe anemia
- Pregnancy
- Beriberi
- Paget’s disease

NY Heart Association classification
Although criticized as being unreliable, this system is still widely used.

Class
I: Ordinary physical activity does not cause symptoms (fatigue, palpitations, dyspnea, or angina).
II: Slight limitation of activity. Ordinary activity causes symptoms.
III: Marked limitation of activity. Mild activity causes symptoms.
IV: Any physical activity causes symptoms. Symptoms at rest.

Treatment
- Clinical trials of heart failure therapy have established the validity of the neurohumoral model of heart failure and discredited the purely hemodynamic model.
- Survival is improved by blockade of the malignant effects of norepinephrine by blockers and of angiotensin II and aldosterone by ACE inhibitors and spironolactone.
- To administer a blocker to a patient with a weak heart defies common sense. However, the beneficial hormonal effects of blockers (catecholamine blockade) outweigh their hemodynamic (negative inotropic) effects.
- It took many negative drug trials to conclude that, for the time being at least, inotropic stimulation is a therapeutic dead end in chronic heart failure.
- Digoxin is the only inotropic agent considered safe in the treatment of heart failure. Mortality increases were seen in trials of several positive inotropic drugs: dobutamine, xamoterol, ibopamine, milrinone, vesnarinone.

Non-pharmacological therapy
- Sodium intake should be limited to 2–3 grams per day.
- Alcohol and excessive fluid intake should be discouraged.
- Patients should walk or bicycle regularly as tolerated.
- Aerobic exercise is favored over isometric exercise.

Angiotensin converting enzyme (ACE) inhibitors
- ACE inhibitors reduce afterload by preventing the formation of the vasoconstrictor angiotensin and the breakdown of the vasodilating bradykinins. They block the malignant effects of angiotensin II (vasoconstriction) and aldosterone (salt and water retention).
- Several ACEIs have been shown to reduce mortality in patients with mild or severe failure and have also been shown to slow the development of symptoms in asymptomatic patients with mildly reduced ejection fractions.
- The ATLAS trial found that, compared with low dose lisinopril (2.5–5 mg/day), high dose lisinopril (32.5–35 mg/day) was associated with an 8% lower risk of death (P = 0.128) and 24% fewer hospitalizations for heart failure (P = 0.002).
- ACE inhibitors should be used in all patients with heart failure due to systolic dysfunction, even if asymptomatic.
- Caution and close monitoring are necessary in patients with:
  - potassium > 5.5 mEq/l
  - systolic blood pressure < 90 mmHg
  - creatinine > 3.0 mg/dl.

Angiotensin receptor blockers (ARBs)
- The Evaluation of Losartan in the Elderly (ELITE) studies have compared the angiotensin II antagonist losartan to the

Cor pulmonale
Enlargement of the right ventricle, sometimes accompanied by right ventricular failure. The most common causes are chronic obstructive pulmonary disease, left sided heart failure, pulmonary emboli, primary pulmonary hypertension, pulmonic stenosis, and tricuspid insufficiency. In pure right sided heart failure, edema, congestive hepatomegaly, and systemic venous congestion are more prominent than pulmonary congestion.

7 The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced ejection fractions. N Engl J Med 1992;327:685–91. The SOLVD prevention trial found that enalapril 10 mg bid reduced the development of symptoms from 30% (with placebo) to 21% (NNT = 11).
ACE inhibitor captopril in two head to head trials, with conflicting results.
- In ELITE I,\(^9\) losartan was associated with less morbidity and mortality than captopril.
- In ELITE II,\(^10\) there were no significant differences in mortality between the losartan group (11.7%) and the captopril group (10.4%) at 1.5 years median follow up.
- There are currently insufficient data to recommend ARBs as first line agents in the treatment of heart failure. They should be used in patients who cannot tolerate ACE inhibitors.
- Because ACE inhibitors achieve only incomplete inhibition of the renin-angiotensin-aldosterone pathway, there is hope that a combination of ACE inhibitors and ARBs will result in better outcomes than ACE inhibitors alone. A preliminary study\(^11\) found that the combination of candesartan and enalapril slightly improved surrogate endpoints: higher ejection fractions and smaller left ventricular volumes.

**β Blockers**
- The most promising new therapy for heart failure. Trials have shown morbidity and mortality benefits commensurate with ACE inhibitors.
- In the US Carvedilol Heart Failure study,\(^12\) carvedilol (a non-selective β and α\(_1\) receptor antagonist with antioxidant properties) showed a dramatic improvement in morbidity and mortality. The overall mortality rate over an average of 6.5 months was 3.2% in the carvedilol group versus 7.8% in the placebo group.
- The second Cardiac Insufficiency Bisoprolol trial (CIBIS-II)\(^13\) showed a survival benefit in stable patients with NYHA class III and IV heart failure.
- In the Metoprolol CR/XL Randomized Intervention Trial (MERIT-HF),\(^14\) long acting metoprolol given once daily improved survival, functional class, hospitalizations, and well being when added to standard therapy.
- A meta-analysis\(^15\) of studies of β blockers in the setting of class IV heart failure showed survival benefit.
- Because β blockers may worsen symptoms initially, they should be started at low doses with close monitoring.
- Pretreatment tachycardia may identify patients with low stroke volumes, in whom initiation of β blocker therapy should be monitored more closely.

**Diuretics**
- Diuretics have been used in the treatment of fluid retention for centuries. Paradoxically, less is known about their therapeutic value and optimal use than about recently introduced drugs.
- Diuretics do not retard the progression of chronic heart failure; their effect on survival is unknown.
Thiazide diuretics are appropriate for patients with mild fluid overload and serum creatinine < 2.5 mg/dl. Patients who have edema on hydrochlorothiazide 50 mg PO qd should be switched to a loop diuretic such as furosemide, started at a dose of 20–40 mg PO qd. In refractory edema, loop diuretics may be administered more than once a day or combined with diuretics that have their effect on different parts of the nephron (hydrochlorothiazide, metolazone). Dosage depends on the patient’s degree of edema, weight, age, renal function, and salt intake. Excessive doses may cause hypotension, fatigue, and azotemia.

**Digoxin**
- The effectiveness of digitalis has been debated since its introduction over 200 years ago.
- The definitive Digitalis Investigation Group trial\(^{16}\) found that digoxin reduced hospitalizations but had no effect on mortality from heart failure.
- A subgroup analysis showed that the patients who benefited most from digoxin were those with ejection fractions < .25, cardiomegaly, and those in NYHA classes III or IV.
- Digoxin is indicated for patients with severe heart failure. It should be added to the regimen of patients with mild or moderate congestive heart failure who are symptomatic on ACE inhibitors and diuretics.

**Spironolactone**
- In the Randomized Aldactone Evaluation Study (RALES),\(^{17}\) 1663 patients with EF < .35 were randomized to receive placebo or spironolactone 25 mg PO qd in addition to their ACE inhibitor, loop diuretic, and (in ~ 75%) digoxin. At two years mean follow up, there were 386 deaths in the placebo group (46%) versus 284 in the spironolactone group (35%). RRR = 0.70, ARR = 0.11, NNT = 9. Mortality in this trial was extremely high.

**Hydralazine plus isosorbide dinitrate**
- Although less effective than ACE inhibitors, the combination of isosorbide dinitrate and hydralazine has also been proven to improve survival and is appropriate in patients who are symptomatic on ACE inhibitors or who cannot take them because of elevations in potassium or creatinine.
- Target doses in the Vasodilator Heart Failure Trial II\(^{18}\) were hydralazine 75 mg PO qid and isosorbide dinitrate 40 mg PO qid.
- Although enalapril improved survival better, the combination of hydralazine and isosorbide was superior in

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“Dropsy”
The historical diagnosis of dropsy referred to fluid overload.

An Account of the Foxglove by William Withering was published in England in 1785.

\(^{16}\) The Digitalis Investigation Group. *The effect of digoxin on mortality and morbidity in patients with heart failure*. *N Engl J Med* 1997;336:525–33. The Digitalis Investigation Group trial randomized 6800 symptomatic patients with ejection fractions < .45 to receive either digoxin or placebo in addition to their ACE inhibitors and diuretics. Over an average follow up of 37 months, mortality was unaffected (34.8% in the digoxin group v 35.1% in the placebo group). Digoxin reduced overall hospitalizations by 6% (26.8% v 34.7%) (NNT = 13).


improving ejection fraction. A combination of three drugs may be useful in patients with severe failure.

**Calcium channel blockers**
- Calcium channel blockers are generally contraindicated in the setting of systolic heart failure.
- In a placebo controlled study\(^\text{19}\) of post-MI patients treated with diltiazem, in those with a baseline ejection fraction of <.40, late heart failure appeared in 12% (39/326) receiving placebo versus 21% (61/297) receiving diltiazem.
- The PRAISE\(^\text{20}\) study of amlodipine showed no increase in cardiovascular morbidity and mortality in patients with ejection fractions <30%. Amlodipine may be used in patients with severe heart failure if necessary for the treatment of angina or hypertension.

**Warfarin**
- In the absence of controlled trials of anticoagulation in patients with dilated cardiomyopathy, routine anticoagulation is not recommended.
- Patients should be anticoagulated for three months after a significant anterior wall myocardial infarction (AMI). The INR target is 2.5 (range 2.0–3.0).

**Risk stratification for sudden death**
- Each year, ~350,000 people experience sudden cardiac death in the US.
- In patients with heart failure, sudden death occurs at 6–9 times the rate of the general population.
- Sudden death due to arrhythmia is the cause of death in 30–40% of heart failure patients.
- Risk stratification tools (signal averaged ECG, Holter monitoring for non-sustained ventricular tachycardia, treadmill ECG) may identify a high risk subgroup who may benefit from electrophysiologic testing and implantable defibrillators.
- Most sudden death in heart failure is initiated by coronary plaque disruption. An aggressive revascularization strategy is indicated in patients with heart failure and coronary artery disease.

**Amiodarone**
- Randomized trials of amiodarone to prevent sudden cardiac death have produced conflicting results.
- A meta-analysis\(^\text{21}\) of 15 randomized trials found that amiodarone modestly reduced all-cause mortality in patients with left ventricular dysfunction by 22%.
- Amiodarone has many serious side effects. The need for a loading dose has recently been questioned.

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Diastolic dysfunction

- Symptoms of heart failure despite an ejection fraction of >50% are consistent with diastolic dysfunction, an inability of the left ventricle to relax properly during diastole.
- A stiff, hypertrophied left ventricle tends to develop abnormally high pressure during diastole, especially during exercise.
- High pressure in the receiving left ventricle during diastole reduces the pressure gradient across the mitral valve, impairs filling efficiency, and lowers cardiac output.
- More dramatically, when left ventricular diastolic pressure exceeds 30 mmHg, hemodynamic forces favor transudation of fluid into the alveoli: pulmonary edema results.
- The principles of long term therapy are:
  - blood pressure control (≤ 140/90) so as to reverse left ventricular hypertrophy
  - maintenance of appropriate blood volume through diuresis
  - slowing of the heart rate to improve filling during diastole.
- Unlike systolic heart failure, diastolic dysfunction has not been studied in large trials. β blockers, calcium channel blockers, diuretics, nitrates, and ACE inhibitors are all used in the therapy of diastolic dysfunction. The optimal therapy is unknown.
- Digoxin has no role in the therapy of pure diastolic dysfunction.

Revascularization

- The goal of angioplasty and bypass surgery is to protect viable myocardium from further damage and to restore function to hibernating myocardium.
- The Coronary Artery Surgery Study (CASS) comparing coronary artery bypass grafting (CABG) to medical therapy found a significant 10 year survival benefit with surgery in patients with initial ejection fractions <.50; however, patients with Class III and IV heart failure were excluded from the study.
- Patients with heart failure and exertional angina should undergo coronary angiography. These patients are the ones most likely to benefit from revascularization.
- Heart failure patients with a history of MI but without angina should undergo periodic exercise stress testing.
- There is no evidence that revascularization benefits heart failure patients without angina or a history of MI. Risk factors for coronary artery disease should be considered when considering stress testing.

Implantable cardioverter/defibrillator

- ICDs have consistently outperformed amiodarone in randomized trials of sudden death prevention.24,25

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23 Alderman EL, Bourassa MG, Cohen LS et al. Ten years follow-up of survival and myocardial infarction in the randomized coronary artery surgery study. Circulation 1990;82:1629–46. 79% of the surgical patients versus 61% of the medical patients were alive at 10 years.


• American College of Cardiology/American Heart Association Guidelines class I indications for ICD placement:26
  —cardiac arrest due to ventricular fibrillation (VF) or ventricular tachycardia (VT) not due to a transient or irreversible cause
  —spontaneous, sustained VT
  —syncope of undetermined origin with inducible VT or VF on electrophysiologic study (EPS)
  —non-sustained VT with previous MI, EF < .35, and inducible VT or VF on EPS.

Heart transplantation
• The prognosis of congestive heart failure with medical treatment is poor. Poor prognostic signs include a third heart sound, conduction delay on ECG, hyponatremia, increased pulmonary capillary wedge pressure, and low peak oxygen consumption (VO₂).
• Between January 1988 and April 1994, the one-year heart transplant patient survival rate was 82.5%; the three-year survival rate was 74.8%. Three-year survival for patients who made it through the first year was 90.6%.27

Indications for transplantation28
• Maximal VO₂ < 14 ml/kg per minute measured during stress testing and major limitation of the patient’s activities.
• Recurrent unstable ischemia limiting routine activity that is not amenable to bypass surgery or angioplasty.
• Recurrent symptomatic ventricular arrhythmias refractory to therapy.
• Instability of fluid balance/renal function not due to patient non-compliance.

Contraindications to transplantation
• Age > 60–65
• Comorbid illness that would affect survival.
• Inability to comply with a complex medical regimen.
• Current drug, alcohol, or tobacco abuse.


In 1999, there were 2185 heart transplants in the US; 770 patients died while on the waiting list. As of February 3 2001 there were 4177 patients on the waiting list.

Investigational therapies
• Implantable left ventricular assist system
• Left ventricular surgical reduction
• Porcine heart transplant
Table 20.1  Selected oral agents for heart failure.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage forms (mg)</th>
<th>Usual dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACE inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enalapril (Vasotec)</td>
<td>2.5/5/10/20</td>
<td>2.5–20 mg PO bid</td>
</tr>
<tr>
<td>Captopril (Capoten)</td>
<td>12.5/25/50</td>
<td>6.25–100 mg PO tid</td>
</tr>
<tr>
<td>Lisinopril (Prinivil, Zestril)</td>
<td>2.5/5/10/20/40</td>
<td>2.5–40 mg PO qd</td>
</tr>
<tr>
<td>Ramipril (Altace)</td>
<td>1.25/2.5/5/10</td>
<td>1.25–10 mg PO qd</td>
</tr>
<tr>
<td><strong>Angiotensin receptor blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Losartan (Cozaar)</td>
<td>25/50/100</td>
<td>25–100 mg PO qd</td>
</tr>
<tr>
<td>Candesartan (Atacand)</td>
<td>4/8/16/32</td>
<td>4–32 mg PO qd</td>
</tr>
<tr>
<td><strong>Diuretics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrochlorothiazide (Esidrix, HydroDiuril)</td>
<td>25/50</td>
<td>25–50 mg PO qd</td>
</tr>
<tr>
<td>Furosemide (Lasix)</td>
<td>20/40/80</td>
<td>20–80 mg PO qd</td>
</tr>
<tr>
<td>Metolazone (Zaroxolyn)</td>
<td>2.5/5/10</td>
<td>2.5–10 mg PO qd</td>
</tr>
<tr>
<td><strong>Inotropes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin (Lanoxin)</td>
<td>0.125/0.25</td>
<td>0.125–0.25 mg PO qd</td>
</tr>
<tr>
<td><strong>β Blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carvedilol (Coreg)</td>
<td>6.25/12.5</td>
<td>6.25–25 mg PO bid</td>
</tr>
<tr>
<td>Bisoprolol (Zebeta)</td>
<td>5/10</td>
<td>5–20 mg PO qd</td>
</tr>
<tr>
<td>Metoprolol (Lopressor)</td>
<td>50/100</td>
<td>25–100 mg PO bid</td>
</tr>
<tr>
<td><strong>Calcium channel blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amlodipine (Norvasc)</td>
<td>2.5/5/10</td>
<td>2.5–10 mg PO qd</td>
</tr>
<tr>
<td><strong>Vasodilators/Nitrates</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydralazine (Apresoline)</td>
<td>10/25</td>
<td>25–75 mg PO tid</td>
</tr>
<tr>
<td>Isosorbide dinitrate (Isordil)</td>
<td>10/20/30/40</td>
<td>20–40 mg PO tid</td>
</tr>
<tr>
<td><strong>Antiarrhythmics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone (Cordarone)</td>
<td>200</td>
<td>400 mg PO qd</td>
</tr>
</tbody>
</table>
### Table 20.2  All-cause mortality data in six placebo controlled heart failure trials.

<table>
<thead>
<tr>
<th>Agent</th>
<th>#</th>
<th>EF</th>
<th>FU</th>
<th>Plac</th>
<th>Rx</th>
<th>RRR</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol (CIBIS II)</td>
<td>2647</td>
<td>≤.35</td>
<td>16</td>
<td>.173</td>
<td>.118</td>
<td>.34</td>
<td>.055</td>
<td>18</td>
</tr>
<tr>
<td>Carvedilol (USCHF)</td>
<td>1197</td>
<td>≤.35</td>
<td>6</td>
<td>.078</td>
<td>.032</td>
<td>.65</td>
<td>.046</td>
<td>22</td>
</tr>
<tr>
<td>Digoxin (DIG)</td>
<td>6800</td>
<td>≤.45</td>
<td>37</td>
<td>.351</td>
<td>.348</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Enalapril (SOLVD)</td>
<td>2569</td>
<td>≤.35</td>
<td>41</td>
<td>.397</td>
<td>.352</td>
<td>.16</td>
<td>.045</td>
<td>22</td>
</tr>
<tr>
<td>Metoprolol (MERIT-HF)</td>
<td>3991</td>
<td>≤.40</td>
<td>12</td>
<td>.072</td>
<td>.109</td>
<td>.335</td>
<td>.037</td>
<td>27</td>
</tr>
<tr>
<td>Spironolactone (RALES)</td>
<td>822</td>
<td>&lt;.35</td>
<td>24</td>
<td>.459</td>
<td>.345</td>
<td>.30</td>
<td>.11</td>
<td>9</td>
</tr>
</tbody>
</table>

#: number of patients
EF: ejection fraction
FU: follow up in months
Plac: mortality rate in the placebo group
Rx: mortality rate in the treatment group
RRR: relative risk reduction
ARR: absolute risk reduction
NNT: number needed to treat
NS: non-significant
21 Hepatitis A, B, and C
Damara Gutnick

Hepatitis A
Epidemiology, diagnosis, and treatment
• In the US, most hepatitis A occurs during community outbreaks. Hepatitis A is endemic in developing countries.
• Transmission is by ingestion of food or water with fecal contamination or by person to person contact.
• Hepatitis A presents with abrupt hepatitis symptoms (nausea, anorexia, jaundice, enlarged tender liver) after an incubation period of about 30 days.
• Diagnosis is by IgM antibodies during the acute phase.
• Hepatitis A is a self limited illness; recovery occurs within 4–8 weeks. Treatment is supportive. There is no chronic carrier state.

Prevention
• Hepatitis A vaccination1 is recommended for travelers to endemic areas, male–male sex partners, IV drug users, healthcare workers, and patients with clotting factor disorders or chronic liver disease.2 The vaccine is thought to be effective for up to two decades.
• Postexposure prophylaxis with immune globulin (0.02 ml/kg) should be administered to unvaccinated persons who have been exposed to hepatitis A within the past two weeks. Hepatitis A vaccination can be given at the same time.
• Travelers can receive immune globulin for immediate protection.

Hepatitis B
Epidemiology
• The yearly rate of infection in the US is estimated at 200 000–300 000. Of these, 250 will die of acute hepatitis B.
• The worldwide prevalence of chronic hepatitis B infection is 0.2%.
• Hepatitis B is transmitted parenterally, sexually, and perinatally.
• Risk factors for hepatitis B include IV drug use, sex with IV drug users, male to male sex, tattooing, body piercing, and hemodialysis.

Diagnosis and natural history
• At 1–4 months following transmission, acute hepatitis symptoms occur in a minority of patients. Most will develop the infection subclinically.
• Diagnosis is by hepatitis B surface antigen (HBsAg) during the acute phase.
• Infectivity is related to the presence of e antigen (HBeAg) and hepatitis B virus DNA (HBV DNA).

• The overwhelming majority of adult patients with acute hepatitis B recover and clear their HBsAg, leaving them with chronic surface antibody (HBsAb).
• About 10% of patients develop a chronic state with persistent HBsAg. Most of these chronic carriers, especially those with normal liver enzymes, have a benign course.3
• The most serious outcomes – cirrhosis, hepatocellular cancer, and death – seem to be associated with high viral activity (HBeAg and HBV DNA).4

Prevention
• Hepatitis B vaccination5 is recommended for all infants and children as well as travelers to endemic areas, male–male sex partners, IV drug users, sexually active homosexuals (with >1 partner or a history of sexually transmitted disease), healthcare workers, prisoners, and patients with clotting factor disorders or chronic liver disease. The vaccine is thought to be effective for at least 10 years.
• Postexposure prophylaxis is achieved mainly with vaccination. Immune globulin (0.06 ml/kg) can be added for perinatal exposure and for known household, parenteral, or sexual contact within two weeks of exposure.
• Pregnant women should be screened during the first trimester for HBsAg and again in the third trimester if at high risk.
• Inadequate response to the vaccination series is sometimes seen in hemodialysis patients, immunocompromised patients, alcoholics, and elderly people. If necessary, postvaccination testing (goal HBsAb titer >10 IU/l) should be performed several months after completion of the vaccine series. An additional 1–3 doses may be required.

Treatment
• Treatment of acute hepatitis B is supportive.
• The goal of treating chronic hepatitis B is to diminish viral activity (clearance of HBeAg and HBV DNA). Alpha Interferon4 and lamivudine6 achieve this in 30–50% of selected patients, but long term benefits in terms of cancer, cirrhosis, and mortality are still being investigated.
• There are some preliminary data suggesting that interferon may be useful in preventing cancer in patients with cirrhosis.7
• Famciclovir has also shown benefit in suppressing viral activity and improving liver histology.8
• In general, patients with persistently elevated liver enzymes, HBeAg, or HBV DNA should be referred to a hepatologist to be evaluated for possible treatment.

Hepatitis C
Epidemiology
• Almost 4 million Americans, or 1.8% of the US population are infected with HCV, but most are asymptomatic and...
undiagnosed. The highest prevalence is in young persons (age 30–49) and African Americans.9

- HCV it is the leading reason for liver transplantation in the US.
- Transmission is primarily parenteral. Intravenous drug use accounts for 50%, and pre-1992 blood transfusion for 10% of hepatitis C infections.10 Perinatal transmission is responsible for about 6% of cases.
- Transmission between monogamous couples is uncommon (3–5%) and it is not clear if use of condoms lowers this rate.11
- Other risk factors include hemodialysis, clotting factor transfusions in hemophiliacs, occupational exposures, sexual promiscuity, tattoos, body piercing, and nasal cocaine use.
- The mode of transmission is unknown in <10% of cases.

Clinical course

- The vast majority of patients with acute HCV ultimately develop chronic infection, but hepatocellular carcinoma and cirrhosis are less common and take decades to develop.12,13 The actual incidence of these serious sequelae has not been established, but for most patients HCV is an indolent disease.14
- ALT is normal in one third of patients, persistently elevated in another third, and waxes and wanes in the remainder.
- Some patients develop extrahepatic manifestations that appear to be autoimmune in nature, such as arthritis, glomerulonephritis, sicca syndrome, and cryoglobulinemia.
- Even moderate alcohol consumption worsens the course of HCV and increases the risk of developing cirrhosis.
- Smoking has also been reported to worsen the course of HCV.
- Concomitant infection with other viral hepatitides can cause fulminant liver failure.15 Patients should be vaccinated against hepatitis A and B.
- Coinfection with HIV also appears to worsen the course of HCV and increase the risk of developing cirrhosis.

Diagnosis

- The most common symptoms of acute infection are malaise, weakness and anorexia, but the majority of patients are asymptomatic.
- HCV antibodies are detected by enzyme immunoassay. Unlike antibodies to hepatitis A and B, these confer no protection.
- Viral load can be quantified by hepatitis C RNA polymerase chain reaction (PCR).
- Additional evaluation should include α fetoprotein, viral genotyping, TSH, and ultrasonography to exclude masses.
- Liver biopsy is indicated when histologic findings will alter treatment decisions (see below).
HEPATITIS A, B, AND C

Treatment

- Goals of treatment are defined in three ways.
  - Virological: no detectable HCV RNA. In most clinical trials, sustained virologic response is defined as undetectable RNA six months after completion of treatment.
  - Biochemical: normalization of ALT
  - Histological: diminished inflammation on biopsy

- Factors predictive of good response to therapy.
  - HCV genotype 2 or 3 (the most important predictor). 16 Most Americans with HCV are infected with genotype 1
  - Low viral load (<2–3 million RNA copies/ml)
  - Mild liver histology.

Patient selection

- The 1997 NIH Consensus Statement11 recommends treatment for those patients at greatest risk for progressing to cirrhosis:
  - Persistently elevated ALT
  - Detectable HCV RNA
  - Liver biopsy showing portal or bridging fibrosis and moderate to severe inflammation and necrosis.

- Patients who should not be treated include:
  - Persistently normal ALT
  - Active users of alcohol or illicit drugs
  - History of major depression, psychosis, suicidal ideation, cytopenias, severe cardiac disease, renal insufficiency, pregnancy.

- Patients with decompensated cirrhosis should be referred for transplantation; however, recurrence of hepatitis C is common.

Treatment efficacy

- The current standard of care is combination therapy with ribavirin and interferon-alpha 2b, which has been shown in a number of trials to suppress HCV RNA.16

- Peginterferon (addition of a polyethylene glycol molecule to interferon) prolongs the half-life, allowing weekly instead of thrice weekly injections, with better response rates than interferon alone.17

- Peginterferon also appears to be superior in patients with compensated cirrhosis or bridging fibrosis.18

- Preliminary data suggest that peginterferon plus ribavirin produces response rates similar to those of regular interferon with ribavirin.19

- Retrospective analyses suggest that interferon treatment may lower the risk of hepatocellular carcinoma.20

- Because patients with genotype 1 are less likely to respond, they are usually treated for 48 weeks; those with genotypes 2 or 3 are treated for 24 weeks.

Side effects of treatment

- Flu-like symptoms occur early in most patients receiving interferon, but generally diminish with continued therapy.

16 McHutchison JG, Gordon SC, Schiff ER et al. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. N Engl J Med 1998;339:1485. 912 patients were randomized to IFN with or without ribavirin. At 48 weeks virological response rates were:

<table>
<thead>
<tr>
<th>Genotype</th>
<th>IFN (%)</th>
<th>IFN/ribavirin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29</td>
<td>9</td>
</tr>
<tr>
<td>2 or 3</td>
<td>65</td>
<td>31</td>
</tr>
</tbody>
</table>

A six-month course of combination therapy with interferon and ribavirin costs almost $20 000.

17 Zeuzem S, Feinman SV, Rasenack J et al. Peginterferon alfa-2a in patients with chronic hepatitis C. N Engl J Med 2000;343:1666–72. 531 patients were randomized to weekly peginterferon (Peg-IFN) or thrice weekly regular IFN. At 72 weeks, sustained virological responses were 39% and 19%, respectively.

18 Heathcote EJ, Shiffman ML, Cooksley GE et al. Peginterferon alfa-2a in patients with chronic hepatitis C and cirrhosis. N Engl J Med 2000;343:1673–80. After 12 weeks of regular IFN, 271 patients with cirrhosis were randomized to 48 weeks of Peg-IFN or continued regular IFN. At 72 weeks, sustained virological responses were 30% and 8%, respectively. In the subset of patients who underwent biopsy (about half), histological responses were 54% v 31%.

19 Manns MP, McHutchison JG, Gordon S et al. Peginterferon alfa2b plus ribavirin compared to interferon alfa2b plus ribavirin for the treatment of chronic hepatitis C; 24 week treatment analysis of a multicenter, multinational phase III randomized controlled trial. Hepatology 2000;32:287A. 1530 patients were randomized to Peg-IFN plus ribavirin (two different regimens) or regular IFN plus ribavirin. At 48 weeks, sustained virological response was 54% in the higher dose Peg-IFN group, v 47% in the low dose and regular IFN groups.

20 Imai Y, Kawata S, Tamura S et al. Relation of interferon therapy and Continued
Fatigue, alopecia, bone marrow suppression, and thyroid and neuropsychiatric effects occur later in therapy.

Treatment with prophylactic antidepressant therapy should be considered in any patient with a history of depression.

Ribavirin can cause hemolytic anemia. It is a known teratogen. Tachycardia may exacerbate pre-existing angina.

**Hepatitis C and HIV**

- HCV infection occurs in as many as a third of patients with human immunodeficiency virus (HIV).\(^{21}\)
- HIV coinfecion increases HCV viral load, the rate of perinatal transmission, and the rate of progression to cirrhosis and death.
- HIV and HCV coinfecion is not a contraindication for highly active antiretroviral therapy or HCV therapy,\(^{22}\) but careful monitoring is needed and referral to a specialist is recommended.


---

**Table 21.1 Agents for viral hepatitis.**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chronic Hepatitis B</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferon-α2b (Intron A) or ...</td>
<td>5 million U SQ qd</td>
<td>16 weeks</td>
</tr>
<tr>
<td></td>
<td>10 million U SQ tiw</td>
<td></td>
</tr>
<tr>
<td><strong>Chronic Hepatitis C</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Genotype I</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferon-α2b (Intron A) plus ...</td>
<td>3 million U SQ tiw</td>
<td>48 weeks</td>
</tr>
<tr>
<td>Ribavirin (Rebetol)**</td>
<td>1000–1200 mg PO qd</td>
<td></td>
</tr>
<tr>
<td><strong>Genotype II, III</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferon-α2b (Intron A) plus ...</td>
<td>3 million U SQ tiw</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Ribavirin (Rebetol)**</td>
<td>1000–1200 mg PO qd</td>
<td></td>
</tr>
<tr>
<td><strong>Vaccines &amp; Immunoglobulins</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis A (Havrix or Vaqta)</td>
<td>1.0 cc IM at 0, 6 months</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B (Recombivax or Engerix-B)</td>
<td>1.0 cc IM at 0, 3, 6 months</td>
<td></td>
</tr>
<tr>
<td>Hepatitis A immune globulin</td>
<td>0.02 ml/kg IM</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B immune globulin</td>
<td>0.06 ml/kg IM</td>
<td></td>
</tr>
</tbody>
</table>

\(^{*}\)HIV status should be assessed before starting lamivudine. HIV positive patients should be referred to a specialist for management.

\(^{**}\)Ribavirin is dosed according to the patient’s weight.
HIV disease
Laurence Peiperl and Dava Klirsfeld

Epidemiology
- The World Health Organization estimates that there are 34.3 million people living with human immunodeficiency virus (HIV). With 2.2 million deaths in 1999, AIDS is now the fourth leading cause of death worldwide.
- Over 95% of HIV infected people live in the developing world.
- 733,374 Americans have been reported with AIDS and 430,441 have died through the end of 1999.
- There are 850,000 Americans living with HIV with 25,000 new infections in 1999.
- There has been tremendous progress in the war against HIV since FDA approval of the first protease inhibitor, ritonavir, in 1996. The number of AIDS deaths in the US has declined steadily from a high of 50,000 in 1995 to 10,000 in 1999.

Diagnosis
HIV testing
- First obtain an ELISA test, a sensitive enzyme linked immunosorbent assay which screens for antibodies against a mixture of HIV proteins. Positive ELISA results are confirmed using the Western blot, a more specific technique that detects antibodies against individual viral proteins.
- When the two tests are not in agreement or the Western blot is indeterminate, an assessment of the patient’s risk and clinical status should be combined with retesting at three, six, and 12 months.
- The combination of ELISA and Western blot has both sensitivity and specificity > 99.9%. False negatives usually result from testing recently infected individuals in the 1–3 month period before detectable antibodies develop.
- Over 95% of infected individuals will develop a positive antibody test by six months following exposure.
- A diagnosis of AIDS is made when an opportunistic infection or neoplasm occurs in an HIV infected person or when the number of T-helper cells (CD4) falls below 200 cells/mm³.

Who should be tested?
- Pregnant women
- Patients with a history of HIV risk:
  - unprotected sex with men and women
  - needle sharing
  - recipient of blood, blood product, or organ between 1980 and 1985 in the US or at any time in a country without HIV screening of blood products and organs.
- Patients with any sexually transmitted disease
- Partners of individuals with known HIV or HIV risk factors
- Children of mothers with HIV born before uniform newborn HIV screening

Individuals who present with signs and symptoms of acute HIV illness and illnesses considered HIV related (for example, unexplained thrush, tuberculosis, recurrent pneumonia).

**T-helper cell (CD4) count**
- Checking a patient’s CD4 count every 3–6 months helps to narrow the differential diagnosis for a given clinical presentation (fever, headache), is useful in deciding when to initiate antiretroviral therapy and prophylaxis against opportunistic infections, and in monitoring the response to antiviral therapy.

**Viral load testing**
- Measures the number of copies of viral RNA per mm$^3$ of plasma.

---

**Table 22.1  T-cell counts at which opportunistic infections and neoplasms occur.**

<table>
<thead>
<tr>
<th>CD4 cells</th>
<th>Infections and neoplasms</th>
<th>Appropriate interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 500</td>
<td>Tuberculosis (pulmonary)</td>
<td>PPD yearly, with INH prophylaxis if indicated</td>
</tr>
<tr>
<td></td>
<td>Histoplasmosis (pulmonary)</td>
<td>High viral load – consider antiviral therapy</td>
</tr>
<tr>
<td></td>
<td>Coccidioidomycosis (pulmonary)</td>
<td>Pneumococcal vaccine (once)</td>
</tr>
<tr>
<td></td>
<td>Cryptosporidiosis (self limited)</td>
<td>Tetanus vaccine q 10 years</td>
</tr>
<tr>
<td></td>
<td>Bacterial pneumonias</td>
<td>Influenza vaccine q year</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hepatitis A and/or B vaccine if non-immune</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pelvic exam, Pap test, GC/Chlamydia q year</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Annual dental exam and RPR</td>
</tr>
<tr>
<td>&lt; 500</td>
<td>Recurrent shingles</td>
<td>As above, plus:</td>
</tr>
<tr>
<td></td>
<td>Kaposi’s sarcoma (cutaneous)</td>
<td>Start antiretrovirals when CD4 &lt; 350</td>
</tr>
<tr>
<td></td>
<td>Non-Hodgkin’s lymphoma (non-CNS)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral candidiasis</td>
<td></td>
</tr>
<tr>
<td>&lt; 200</td>
<td><em>Pneumocystis carinii</em> pneumonia</td>
<td>As above, plus:</td>
</tr>
<tr>
<td></td>
<td>Tuberculosis (disseminated)</td>
<td>Start PCP prophylaxis</td>
</tr>
<tr>
<td></td>
<td>Histoplasmosis (disseminated)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Coccidioidomycosis (disseminated)</td>
<td></td>
</tr>
<tr>
<td>&lt; 100</td>
<td>Toxoplasmosis (usually encephalitis)</td>
<td>As above, plus:</td>
</tr>
<tr>
<td></td>
<td>Cryptococcosis (usually meningitis)</td>
<td>Start Toxoplasma prophylaxis if not on</td>
</tr>
<tr>
<td></td>
<td>Cytomegalovirus (retina, GI, neuro)</td>
<td>Bactrim for PCP prophylaxis</td>
</tr>
<tr>
<td></td>
<td>Esophageal candidiasis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bacillary angiomatosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cryptosporidiosis (intractable)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Progressive multifocal leukoencephalopathy</td>
<td></td>
</tr>
<tr>
<td>&lt; 50–75</td>
<td><em>Mycobacterium avium</em> complex</td>
<td>As above, plus:</td>
</tr>
<tr>
<td></td>
<td>CNS lymphoma</td>
<td><em>Mycobacterium intracellulare</em> complex prophylaxis</td>
</tr>
<tr>
<td></td>
<td>Kaposi’s sarcoma (visceral)</td>
<td>Consider CMV prophylaxis for CMV positives</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Opthalmalogic exam every 3–4 months</td>
</tr>
</tbody>
</table>

---


Acute infectious diseases, herpes outbreaks, and vaccinations are all associated with a transient increase in viral loads over 3–6 weeks; viral load testing should be avoided during this period.
Levels of >15,000 are associated with impending progression of disease, even in the presence of high CD4 counts.

Viral loads are used to monitor the effectiveness of antiviral therapy.

The RNA PCR method is the FDA approved technique of viral load testing. HIV RNA PCR, however, may miss some subtypes of HIV, particularly the non-clade B subtypes prevalent in patients from Asia and Africa.

The branched-chain DNA method should be used to follow viral load in patients with the non-clade B subtype of HIV.

**History and physical exam**

- Guided by the presenting complaint and CD4 count.
- Skin, lymph nodes, sinuses, oral mucosa, mental status, neurologic exam, ophthalmologic, genital, and psychosocial evaluation merit particular attention.
- Travel history, substance use history, partner notification and domestic violence screening are very important aspects of the initial history.

**Screening tests**

- **RPR or VDRL:** annually. Safety in sexual practices should be encouraged.
- **Hepatitis B antibodies:** if surface antibody negative, vaccinate patients at risk.
- **Hepatitis A antibodies:** vaccinate if negative and if hepatitis C or B infected and/or at risk.
- **PPD:** The earlier, the better. If PPD is negative, repeat annually. Routine anergy testing has not been found to be useful in most settings and is no longer recommended.
- **Pap smear:** should be performed every six months, given the increased rate of persistent HPV infection in HIV infected women.
- **GC/Chlamydia probe:** perform routinely on women when doing Pap, perform on men if symptomatic.
- **Toxoplasma antibody:** usually done with initial labs; if negative, repeat when the CD4 count reaches 100. Useful in prophylaxis decisions and differential diagnosis when CD4 < 100.
- **Glucose 6-phosphate dehydrogenase (G6PD):** usually done with initial labs. If abnormally low, avoid oxidant drugs (dapsone, primaquine), as methemoglobinemia and hemolysis may occur.
- **Lactate dehydrogenase (LDH):** often done as a baseline to facilitate future diagnosis of PCP or lymphoma, both associated with increased LDH.
- **CBC with differential and platelets, electrolytes, BUN, creatinine, and liver panel:** usually done as baseline tests even in asymptomatic patients with HIV. Many clinicians also obtain a baseline chest radiograph.
- **Yearly fundoscopy** for patients with greater than 50–100 CD4 cells and q 3–4 months retinal exam by ophthalmologist for

These tests are appropriate in the assessment of patients with HIV regardless of CD4 count, except where noted.


Also consider:

- **CMV antibody:** the vast majority of IV drug users and homosexual men with HIV are also infected with CMV; nonetheless, if an HIV patient is known to be CMV negative, the use of CMV free blood products is clearly indicated. In addition, prophylaxis against CMV retinitis (see below) need only be considered in patients with evidence of CMV infection by antibody or culture.

VZV antibody: exposure of non-immune immunocompromised persons to varicella zoster virus can result in life threatening disseminated infection. VZV negative patients should avoid such exposure and should promptly receive varicella zoster immune globulin (VZIG) if exposure occurs. Thus, the live virus varicella vaccine should not be used in HIV infected patients.
patients with less than 50–100 cells for early identification of CMV retinitis.

- Consider yearly or biannual anal Pap smears for those with evidence of HPV or history of anal intercourse.
- Hepatitis C antibody: hepatitis C coinfection, particularly in IV drug users, is quite common.

Prevention

Advance directives (living will and/or healthcare proxy)
- Can avert a great deal of suffering. Each patient should be encouraged to establish an advance directive before a medical emergency develops.

Vaccines
- Should be given as early in the course of HIV infection as possible. While benefit is not proven, the following vaccines are usually recommended.
  1. Pneumococcal vaccine in all patients. Consider revaccination every five years.
  2. Hepatitis A and B vaccine in unexposed patients at risk of exposure
  3. Influenza vaccine (in late autumn)
  4. Tetanus vaccine
- Note: Live vaccines (BCG, oral polio, yellow fever, varicella) should be avoided.

Prophylaxis against opportunistic infections
- Primary prophylaxis: to prevent first occurrence of disease.
- Secondary prophylaxis: to prevent recurrence of disease

Pneumocystis carinii pneumonia (PCP)
- When to use primary prophylaxis: CD4 < 200 or unexplained fevers > 2 weeks or thrush. Prophylaxis can be discontinued if the CD4 count remains > 200 for > 6 months.
- What to use: trimethoprim-sulfamethoxazole (TMP-SMZ, Bactrim, Septra) is the treatment of choice. Side effects include neutropenia, rash, GI upset. Alternatives include dapsone, atovaquone, dapsone/pyrimethamine/leucovorin, or aerosolized pentamidine. Prophylaxis can be discontinued if the CD4 count remains > 200 for 3–6 months.
- Secondary prophylaxis: required for life. Agents are the same as above. TMP-SMZ is best; consider desensitization regimen for allergic patients if the prior allergic reaction was not serious.

Toxoplasmosis
- Prevention of exposure: avoid undercooked beef, lamb, pork, venison. Change cat litter daily; use gloves; keep cats indoors; do not feed them raw meat. Wash fruits and vegetables.
- When to use primary prophylaxis: CD4 < 100 and Toxoplasma IgG positive

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8 Several studies have documented temporary but marked increases in HIV viral loads within a few weeks following vaccination of HIV positive patients with common recall antigens, such as tetanus. Although the clinical significance of this burst of viral activity is unknown, some clinicians prefer to use only those vaccines most likely to be of benefit, such as pneumococcus. Stanley SK, Ostrowski MA, Justement JS et al. Effect of immunization with a common recall antigen on viral expression in patients infected with human immunodeficiency virus type I. N Engl J Med 1996;334:1222–30.


10 Bozette SA, Finkelstein DM, Spector SA et al. A randomized trial of three antipneumocystis agents in patients with advanced human immunodeficiency virus infection. NIAID AIDS Clinical Trials Group, N Engl J Med 1995;332:693–9. Three-year relapse rates were 18% for trimethoprim-sulfamethoxazole and 17% for dapsone. For dapsone, 100 mg qd was more effective than 50 mg qd.

Annual risk of a first episode of PCP when CD4 < 200 is about 20% per year without prophylaxis. TMP-SMZ, if tolerated, reduces risk to < 5%. Aerosolized pentamidine, dapsone, and atovaquone each reduce risk to about 10%. Annual risk of recurrent PCP is 60% without prophylaxis. Risk is reduced to about 5% with TMP-SMZ and about 20% with aerosolized pentamidine, dapsone, or atovaquone. Hardy WD, Feinberg J, Finkelstein DM et al. A controlled trial of trimethoprim-sulfamethoxazole or aerosolized pentamidine for secondary prophylaxis of Pneumocystis carinii pneumonia in patients with the acquired immunodeficiency syndrome: ACTG protocol 021. N Engl J Med 1992;327:1842–8.
• **What to use**: TMP-SMZ or dapsone/pyrimethamine/leucovorin (side effects: myelosuppression, rash)

• **Secondary prophylaxis**: required for life: pyrimethamine/[either sulfadiazine or clindamycin]/leucovorin. Pyrimethamine/sulfadiazine/leucovorin is also protective against PCP.

**Tuberculosis**

- **Prevention of exposure**: airborne precautions (including masks) in settings involving known or suspected TB

- **Indications for prophylaxis**: PPD positive (≥ 5 mm induration in HIV positive patients) or a reliable history of an untreated positive PPD at any time in the past with a negative chest radiograph and no clinical evidence of active TB. Also close contacts of persons with infectious TB regardless of PPD result once active disease is excluded.

- **What to use**: INH/pyridoxine for 9–12 months. Side effects include hepatitis and neuropathy. Start after the first trimester in HIV positive pregnant patients. In cases of exposure to multidrug resistant TB, at least two drugs to which the source strain is susceptible should be used. Alternatives include rifampin or rifabutin plus pyrazinamide for two months or rifampin alone for four months.⁹

• **Secondary prophylaxis**: is not indicated.

**Mycobacterium avium complex (MAC)**

- **Prevention of exposure**: none recommended

- **Indications for prophylaxis**: CD4 < 50–75, and no evidence of disseminated MAC (rule out by blood culture) or active TB

- **What to use**: clarithromycin 500 mg PO bid or azithromycin 1200 mg PO q week. Alternatively: rifabutin 300 mg PO qd (many drug interactions and side effects). Primary prophylaxis can probably be discontinued if CD4 ≥ 100 for 3–6 months.¹¹

• **Secondary prophylaxis**: consists of lifelong continuation of the drug combination used to treat disseminated MAC, usually clarithromycin plus one or two other drugs (ethambutol, levofloxacin, rifabutin).

- Although primary prophylaxis recommendations for CMV and systemic mycoses are controversial, secondary prophylaxis is clearly required, generally for the life of the patient.

**Candidiasis**

- **Prevention of exposure**: none known

- **Primary prophylaxis**: not recommended, due to fear of drug resistant Candida (already a problem in some areas), drug interactions, and cost. Symptomatic infections are usually easily treated and rarely serious.

- **Secondary prophylaxis**: may be used if recurrences are frequent or severe. Topical treatments are preferable (clotrimazole, nystatin). Patients with documented esophageal

candidiasis, especially recurrent, should be considered for fluconazole suppression.

**Systemic mycoses**
- **Prevention of exposure:** avoid contaminated sites in endemic areas.
- **Indications for prophylaxis:**
  - Cryptococcus: consider fluconazole prophylaxis for CD4 <50; not generally recommended because of infrequency of disease, cost, and potential for development of resistance
  - Histoplasma: itraconazole is investigational in endemic areas
  - Coccidioides: fluconazole is investigational in endemic areas.

**Systemic mycoses: secondary prophylaxis**
- Required for life
  - Cryptococcus, Coccidioides: fluconazole
  - Histoplasma: itraconazole
  - Amphotericin B is generally only used if these oral regimens fail, the patient is intolerant or pregnant.

**Cytomegalovirus (CMV)**
- **Prevention of exposure:** safe sex, good hygienic practices in childcare centers. Patients at low risk for CMV infection (no male homosexual contact or injection drug use) should be tested for CMV antibody; if negative, they should receive only CMV negative blood products if transfusion is required.
- **When and if to give prophylaxis:** early detection is facilitated by regular fundoscopic exams (q 6–12 months when CD4 <100.) Patients with CD4 <200 should screen their vision regularly (by reading newsprint) and report any loss of acuity to their physician. Oral ganciclovir as primary prophylaxis remains controversial, but may be of benefit in patients with evidence of CMV infection (antibody or culture), not end organ disease and CD4 50–100.

**CMV: Secondary prophylaxis**
- Oral or IV ganciclovir (myelosuppressive) or IV foscarinet (nephrotoxic, may cause severe electrolyte disorders).
- Cidofovir has the advantage of infrequent (every two weeks) administration. It is nephrotoxic and must be used with probencid. Required for life.
- Ganciclovir sustained release implant plus oral ganciclovir
- Fomivirsen intravitreal injection every 2–4 weeks

**Herpesviruses:** herpes simplex (HSV) and varicella zoster (VZV)
- **Prevention of exposure:**
  - HSV – safe sex; avoid active orolabial or genital lesions
  - VZV – if no history of chickenpox or VZV seronegative, avoid exposure to persons with chickenpox or shingles.

Many authorities advocate the initiation of antiviral therapy for any patient with detectable viral load.


is currently recommended in the setting of serious occupational exposure.

**Symptomatic and asymptomatic individuals with CD4**

- These patients have been shown to benefit from antiviral treatment in terms of disease progression and survival and should be offered antiviral treatment; however, the exact optimal time to start is not currently known.
- The clear association between high viral loads and accelerated decline in T-cells has led to the recommendation that antiviral therapy be initiated in all patients with HIV viral loads of >55,000 copies of HIV RNA per ml of plasma or 30,000 copies by branched DNA assay.
- Some studies suggest that, at a given viral load, CD4 counts decline more quickly in women than in men. At this time, therapy initiation guidelines are not different for women but this may change.

**Primary HIV**

- There are data to suggest that treatment of primary HIV infection with combination therapy has a beneficial effect on virologic and clinical endpoints.
- Primary HIV infection “seroconversion illness” usually occurs 1–3 weeks after exposure to HIV. Signs include fever, diffuse lymphadenopathy, maculopapular eruption on trunk, face, palms and soles, mucosal ulcers, pharyngitis, and aseptic meningitis.
- Diagnosis of HIV seroconversion illness is made by measuring an HIV RNA PCR (generally very high) which is detectable, a negative antibody test and the proper clinical setting. HIV RNA PCR is not used as a diagnostic test in other clinical situations. If one suspects HIV seroconversion illness, an infectious diseases consult should be requested immediately.
- Antiviral treatment initiated early in the course may reduce the risk of progression and entry into sequestered sites and may be more effective because of the viral homogeneity.

**Choosing an antiviral regimen**

The choice of an antiviral regimen is often complicated. While a full discussion of the decision making process would require many pages, major contributing factors may be summarized as follows.

**Patient non-adherence and selection of drug resistance**

- Effective combination therapy can result in suppression of plasma HIV to undetectable levels for years, literally halting the progression of disease. However, the regimens that have been shown to achieve this result involve multiple daily doses of several medications, often with strict timing and dietary restrictions.

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Guidelines have recently been changed to a lower CD4 and higher viral load threshold for treatment in order to account for long term toxicities of medications: hyperlipidemia, diabetes, lactic acidosis, and osteoporosis.
Generally one chooses a backbone of two NRTIs and a third drug (either an NNRTI, a protease inhibitor, or abacavir).

If medications are taken at inadequate or irregular doses, detectable viral resistance can emerge over as little as two weeks, resulting in the ultimate failure of the regimen.

Viral strains resistant to certain protease inhibitors, nucleoside analogs, or NNRTIs may prove resistant to some or all other drugs in the same class (“cross-resistance”), leaving the patient with no effective treatment options even if strict adherence becomes possible later.

**Side effects**

- In addition to simple inconvenience, antiviral drugs may cause cytopenias (AZT), neuropathies (ddI, d4T), rash (including Steven–Johnson syndrome with nevirapine), pancreatitis (ddI), diarrhea or GI upset (ritonavir, nelfinavir, ddi), kidney stones (indinavir), and hepatitis (almost any antiviral), to name a few. Combining these drugs may compound the side effects.
- Metabolic abnormalities are probably related to the medications, but may also be from HIV infection itself. Lipodystrophy, hyperlipidemia, insulin resistance, osteoporosis, and osteonecrosis have been associated with regimens including protease inhibitors and, to a lesser extent, regimens containing NNRTIs. Life threatening, insidious-onset lactic acidosis with hepatic steatosis can be caused by NRTIs, probably as a result of mitochondrial toxicity. NRTIs can inhibit mammalian mitochondrial DNA synthesis.

**Drug interactions**

- It is crucial to look at the list of drug interactions for each antiviral before prescribing.
- There are many complex and unpredictable interactions between the protease inhibitors ritonavir, indinavir, and nelfinavir; the NNRTIs; and drugs that are metabolized by the cytochrome P450 mono-oxygenase system (clarithromycin, fluconazole, phenytoin, etc.).
- AZT and D4T should not be used together.
- NNRTIs can affect the metabolism of PIs and drugs metabolized by the P450 system. For example, efaviranz decreases saquinavir levels, ritonavir increases saquinavir and indinavir levels, delavirdine increases nelfinavir levels.

**Prior antiviral history**

- In general, effective treatment requires the simultaneous introduction of at least two but generally three antiretrovirals to which the patient does not harbor resistant viral strains.

**Changing therapy**

- Little evidence exists to support any particular algorithm for changing or adding to existing, tolerated antiretroviral...
therapy. The idea of using viral load thresholds (for example, 5000–10,000 RNA copies/ml) to prompt change in treatment is increasingly attractive, although foundation in clinical data is incomplete.

- Generally, viral loads should be checked every 3–4 months when the patient is stable and every 3–4 weeks when starting or changing therapy.
- When changing a failing regimen, at least two new drugs should be added with different resistance profiles from the drugs that have failed, but a totally new three-drug regimen is preferable.
- The use of resistance testing is not completely clear. Some study results support the use of resistance testing when making decisions regarding changes in therapy, but there is no consensus. Genotypes and phenotypes can be helpful but antiviral therapeutic history must also be taken into account.
- Medications are unlikely to be fully effective if reintroduced. Past incompletely suppressive therapy will most likely have resulted in the selection of virus resistant to the medication used and such resistant strains tend to persist in small numbers.
- In general, one should never add a single drug to a failing regimen (viral load increasing or never significantly suppressed). A new maximally suppressive combination should be started. It is not clear whether “intensification”, which is the addition of one drug to a successful but not completely suppressive regimen, is beneficial or harmful.

Individual goals

- Complete viral suppression is always a fine goal, but certain patients will express or demonstrate inadequate motivation or ability to adhere to a complicated regimen.
- Since reduction in viral load results in clinical benefit even if undetectable levels are not achieved, one is sometimes faced with the choice of initiating a suboptimal therapy that may well lead to selection of resistance versus no treatment at all. The hope is that simpler regimens will become available before the patient’s condition deteriorates. In this situation it should be noted that 3TC is associated with rapid emergence of viral resistance when used in incompletely suppressive regimens, but is an important component of combination therapy.
- Protease inhibitors are highly effective in combination with nucleoside analogs, but can lead to class resistance over weeks to months if used alone or in inadequate combinations. Therefore, the initial use of 3TC and of protease inhibitors should be reserved for regimens intended to be fully suppressive.
- For patients with sustained low viral loads on dual nucleoside regimens (for example, AZT + 3TC, recommended as initial therapy in the past), the benefit of changing versus continuing is unclear.

The choice of regimen in any given situation requires increasing expertise as more information and treatment options become available. An infectious diseases specialist should be consulted in individual cases.

Genotypes and phenotypes detect mutations in virus present in plasma, but cannot detect mutants in proviral form in cells.

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Table 22.2 Medications against HIV.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage forms</th>
<th>Usual dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nucleoside reverse transcriptase inhibitors (NRTIs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abacavir (Ziagen)</td>
<td>300 mg tablets</td>
<td>300 mg PO bid</td>
</tr>
<tr>
<td>Combivir</td>
<td>(Zidovudine 300 mg + lamivudine 150 mg)</td>
<td>1 tab PO bid</td>
</tr>
<tr>
<td>Didanosine (ddI, Videx)</td>
<td>100 mg tablets</td>
<td>200 mg PO bid if ≥ 60 kg</td>
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<tr>
<td></td>
<td></td>
<td>125 mg PO bid if &lt; 60 kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>400 mg PO qd if enteric coated (ddI EC)</td>
</tr>
<tr>
<td>Lamivudine (3TC, Epivir)</td>
<td>150 mg tablets</td>
<td>150 mg PO bid</td>
</tr>
<tr>
<td>Stavudine (d4T, Zerit)</td>
<td>40 mg capsules</td>
<td>40 mg PO bid</td>
</tr>
<tr>
<td>Zalcitabine (ddC, Hivid)</td>
<td>0.75 mg tablets</td>
<td>0.375 or 0.75 mg PO tid</td>
</tr>
<tr>
<td>Zidovudine (AZT, Retrovir)</td>
<td>300 mg tablets</td>
<td>Usual antiviral dose:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>300 mg PO bid</td>
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<tr>
<td></td>
<td></td>
<td>Postexposure prophylaxis:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AZT 200 PO mg tid or</td>
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<tr>
<td></td>
<td></td>
<td>300 mg PO bid plus</td>
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<tr>
<td></td>
<td></td>
<td>lamivudine PO 150 mg bid +</td>
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<tr>
<td></td>
<td></td>
<td>indinavir mg 800 mg PO tid or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>nelfinavir 750 mg PO tid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prevention of fetal transmission</td>
</tr>
<tr>
<td></td>
<td></td>
<td>As part of combination regimen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>during gestation (may wish to</td>
</tr>
<tr>
<td></td>
<td></td>
<td>start at second trimester); IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>during labor; PO to infant</td>
</tr>
<tr>
<td><strong>Protease inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amprenavir (Agenerase)</td>
<td>50, 150 mg capsules</td>
<td>1200 mg PO bid</td>
</tr>
<tr>
<td>Indinavir (Crixivan)*</td>
<td>400 mg capsules</td>
<td>800 mg PO q8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 hour before or 2 hours after</td>
</tr>
<tr>
<td></td>
<td></td>
<td>meals</td>
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<tr>
<td></td>
<td></td>
<td>Patients should drink 1.5 l of</td>
</tr>
<tr>
<td></td>
<td></td>
<td>water a day to prevent kidney</td>
</tr>
<tr>
<td></td>
<td></td>
<td>stones.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Can be given as 800 mg bid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>if used with ritonavir 200 mg bid.</td>
</tr>
<tr>
<td>Nelfinavir (Viracept)</td>
<td>250 mg tablets</td>
<td>750 mg PO q8 or 1250 mg PO q12</td>
</tr>
<tr>
<td>Ritonavir (Norvir)</td>
<td>Liquid: 7.5 ml = 600 mg</td>
<td>600 mg PO q12 with meals</td>
</tr>
<tr>
<td></td>
<td>100 mg tablets</td>
<td>Start at 300 bid; ↑ 100 mg at a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>time over 2 wks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Many drug interactions.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hepatotoxicity, GI upset.</td>
</tr>
<tr>
<td>Saquinavir hard capsules (Invirase)</td>
<td>200 mg capsules</td>
<td>Poorly bioavailable; being</td>
</tr>
<tr>
<td></td>
<td></td>
<td>replaced by soft gel formulation</td>
</tr>
</tbody>
</table>

HIV DISEASE
**Table 22.2  continued**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage forms</th>
<th>Usual dosage</th>
</tr>
</thead>
</table>
| Saquinavir soft gel formulation (Fortovase)    | 200 mg capsules          | 1200 mg PO q8 with meals  
|                                                |                          | Can be given as 400 mg  
|                                                |                          | bid if used with ritonavir  
|                                                |                          | 400 mg bid  
|                                                |                          | Levels are significantly reduced  
|                                                |                          | by Sustiva  |
| Lopinavir/ritonavir combination (Kaletra)      | 133 mg lopinavir/33 mg  | 400 mg lopinavir/100 mg  
|                                                | ritonavir capsule         | ritonavir (3 capsules bid).  
|                                                |                          | Must give 4 capsules bid if  
|                                                |                          | used with Sustiva  |

*Non-nucleoside reverse transcriptase inhibitors (NNRTIs)*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage forms</th>
<th>Usual dosage</th>
</tr>
</thead>
</table>
| Delavirdine (Rescriptor) | 100 mg tablets | 400 mg PO tid  
|                     |              | Can cause strange dreams  
| Efavirenz (Sustiva) | 200 mg capsules | 600 mg PO qHS  
|                    |              | Bedtime dosing is recommended because the drug can cause  
|                    |              | dizziness and a “spacy feeling”  
| Nevirapine (Viramune) | 200 mg tablets | 200 mg PO qd for 14 days,  
|                    |              | then bid if tolerated  
|                    |              | Not to be used for postexposure prophylaxis  |
### Box 22.1 Drugs for opportunistic infections

**Pneumocystis carinii**

**Primary or secondary prophylaxis**

- TMP-SMZ (Bactrim DS)
  - 1 double strength tablet PO qd
- Dapsone
  - 50–100 mg PO qd
  - ± pyrimethamine 50 mg PO q wk + folinic acid (leucovorin) 25 mg PO q wk
    - Can cause hemolytic anemia in patients deficient in G6PD
- Pentamidine (aerosolized)
  - 300 mg q month via Respirgard II jet nebulizer
- Atovaquone (Mepron) suspension
  - 750 mg (= 1 tsp) PO bid with food

**Toxoplasma gondii**

**Primary prophylaxis**

- Either of the first two *Pneumocystis* prophylaxis regimens above

**Chronic suppression**

- Pyrimethamine
  - 25–50 mg PO qd  
  - plus ...
- Sulfadiazine
  - 1 g PO bid  
  - or if sulfadiazine is not tolerated ...
- Clindamycin
  - 300 mg PO qid  
  - and ...
- Folinic acid (leucovorin)
  - 10 mg PO qd

**Cytomegalovirus**

**Chronic suppression**

- Ganciclovir (DHPG)
  - 5 mg/kg IV qd
  - All CMV drugs require dose adjustments for renal insufficiency
- Foscarnet
  - 90–120 mg/kg IV qd via infusion pump only
  - Active diuresis is necessary during administration
- Ganciclovir (oral)
  - 1000 mg PO tid
- Cidofovir (Vistide)
  - 5 mg/kg IV q 2 wks with probenecid

**Herpes simplex virus**

**Chronic suppression**

- Acyclovir
  - 400 mg PO bid
- Famciclovir (Famvir)
  - 500 mg PO bid

**Mycobacterium avium complex**

**Primary prophylaxis**

- Azithromycin (Zithromax)
  - 1200 mg PO q wk
<table>
<thead>
<tr>
<th>Box 22.1 Continued</th>
</tr>
</thead>
</table>
| Clarithromycin (Biaxin)  
500 mg PO bid |
| Rifabutin (Mycobutin)  
300 mg PO qd  
Interactions with protease inhibitors (consult with specialist) |

**Chronic suppression**

Clarithromycin  
500 mg PO bid *plus ≥ 1 of the following:*

- **Ethambutol**  
15 mg/kg PO qd
- **Ciprofloxacin**  
500 mg PO bid
- **Rifabutin**  
300 mg PO qd  
Interactions with protease inhibitors (consult with specialist)

**Mycobacterium tuberculosis**

**Postexposure prophylaxis**

- **Isoniazid (INH)**  
300 mg PO qd × 1 yr *plus*
- **Pyridoxine (vitamin B6)**  
25–50 mg PO qd × 1 yr

For current or past untreated PPD reaction >5 mm or exposure to active TB, or anergic at high risk

**CHRONIC SUPPRESSION OF FUNGAL INFECTIONS**

**Candida albicans**

- **Clotrimazole (Mycelex)**  
10 mg troche dissolved in mouth over 15–30 min 3–5 × /d for thrush
- **Nystatin**  
200,000 U tablet dissolved in mouth 5 × /d for thrush
- **Fluconazole (Diflucan)**  
100 mg PO qd for esophagitis  
*More effective than ketoconazole 200 mg PO qd*

**Cryptococcus neoformans, Coccidioides immitis**

- **Fluconazole (Diflucan)**  
200 mg PO qd

**Histoplasma**

- **Itraconazole (Sporanox)**  
200 mg PO bid
Hyperlipidemia
Nate Link and Michael Tanner

Epidemiology
US Prevalence (%) of Total Cholesterol ≥ 240 mg/dl and Coronary Artery Disease (NHANES III: 1988–94)\(^1\)

<table>
<thead>
<tr>
<th>Age</th>
<th>Cholesterol ≥ 240</th>
<th>Coronary artery disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>20–34</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>35–44</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>45–54</td>
<td>25</td>
<td>23</td>
</tr>
<tr>
<td>55–64</td>
<td>25</td>
<td>37</td>
</tr>
<tr>
<td>65–74</td>
<td>22</td>
<td>39</td>
</tr>
<tr>
<td>≥ 75</td>
<td>14</td>
<td>32</td>
</tr>
</tbody>
</table>

- For persons ≥ 20, the prevalence of cholesterol ≥ 240 mg/dl was 18%.
- Note the marked increase in hypercholesterolemia rates for women after menopause.

Factors that influence lipid values
- **Acute myocardial infarction**: transient decrease in LDL-C and total cholesterol (nadir 1–2 weeks after MI). TGs peak three weeks after MI. Values return to baseline in about six weeks.
- **Pregnancy**: TC increases by up to 75% (to a mean of level of 315 mg/dl) and does not return to normal for six months.
- **Smoking**: decreases HDL-C
- **Physical activity**: increases HDL-C, decreases TGs
- **Alcohol**: increases HDL-C and TGs

Diagnosis
Screening recommendations
- There is no direct evidence to support routine screening of cholesterol. The need to do so is supported by the asymptomatic nature of hyperlipidemia and the effectiveness of treatment.
- **National Cholesterol Education Program** (2001): routine measurement of lipids in all adults age 20 or older at least once every five years.

Determining the patient’s LDL-C goal
Assess risk factors
- Age: males ≥ 45 and females ≥ 55
- Hypertension (BP ≥ 140/90 mmHg or on antihypertensive medication)
- Cigarette smoking
- Family history of premature CAD (definite MI or sudden death in a father or brother < 55 or in a mother or sister < 65).

Cholesterol conversion factor
1 mmol/l = 38.6 mg/dl

Glossary
- TC = total cholesterol
- LDL-C = low density lipoprotein cholesterol
- HDL-C = high density lipoprotein cholesterol
- TGs = triglycerides
- FAs = fatty acids

A national success story
Mean serum total cholesterol levels in Americans aged 20–74 declined from 220 to 205 mg/dl in the years 1960 to 1991. The peak year of the 20th century American atherosclerosis pandemic was 1963, when the prevalence of coronary artery disease reached 220 cases per 100,000.


Low HDL-C level (<40 mg/dl). A high HDL-C level (≥60) is a negative risk factor and cancels out another risk factor.

**Calculate the 10-year risk for coronary artery disease**
See tables 23.4 and 23.5

**Identify the LDL-C treatment target**
Coronary artery disease or equivalent LDL-C < 100

- Diabetes
- 10-year CAD risk >20%
- Symptomatic carotid artery disease
- Peripheral arterial disease
- Abdominal aortic aneurysm

Two or more CAD risk factors LDL-C < 130

Less than two CAD risk factors LDL-C < 160

**Compare to ATP III LDL-C thresholds for treatment**

<table>
<thead>
<tr>
<th></th>
<th>Goal</th>
<th>TLC</th>
<th>Meds</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1 risk factors</td>
<td>160</td>
<td>≥160</td>
<td>≥190</td>
</tr>
<tr>
<td>≥2 risk factors; &lt;10%</td>
<td>130</td>
<td>≥130</td>
<td>≥160</td>
</tr>
<tr>
<td>10-year CAD risk</td>
<td>130</td>
<td>≥130</td>
<td>≥130</td>
</tr>
<tr>
<td>≥2 risk factors; 10–20%</td>
<td>100</td>
<td>≥100</td>
<td>≥130</td>
</tr>
<tr>
<td>CAD or equivalent</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Drug therapy is optional for patients who are slightly (0–30 mg/dl) over target despite therapeutic lifestyle changes (TLC). APT III’s approach to drug therapy is more aggressive than the 1993 NCEP II guideline, which reserved drugs for patients >30 points over target.

**Dietary treatment**

- The recommended first line of therapy for hyperlipidemia is the American Heart Association Step I and Step II diet approach.

**Step I diet**
- <300 mg cholesterol/day (1 egg = 300 mg)
- <30% total calories from fat
- <10% total calories from saturated fat

**Step II diet**
- <200 mg cholesterol/day
- <7% total calories from saturated fat

**Effect of Step I and Step II Diets on Serum Lipids**

<table>
<thead>
<tr>
<th>Diet</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step I</td>
<td>−12%</td>
<td>−2%</td>
<td>−8%</td>
</tr>
<tr>
<td>Step II</td>
<td>−16%</td>
<td>−7%</td>
<td>−8%</td>
</tr>
</tbody>
</table>

Growing evidence supports the importance of exact composition rather than total amount of dietary fats. The preferred proportions of monounsaturated, n-3 and n-6 polyunsaturated, and trans FAs have not yet been determined.

**Formula for calculating LDL-C**

\[ \text{LDL-C} = \text{TC} - (\text{HDL-C} + \text{TG}/5) \]

TGs rise postprandially; therefore, a non-fasting sample will falsely depress LDL-C levels. If TGs are >400 mg/dl, LDL-C must be measured directly by ultracentrifugation.

**Secondary causes of hyperlipidemia**
- Diabetes mellitus
- Hypothyroidism
- Obesity
- Cholestasis
- Nephrotic syndrome
- Alcoholism

**Step I highlights**: Daily limit of 2 cups of 1% milk; 3 ounces of lean meat; 4 tablespoons of margarine or vegetable oil; and 2 ounces low fat cheese, cream cheese, or mayonnaise.

**Step II highlights**: Decrease milk to 1 cup skim, decrease lean meat to 2 ounces, decrease low fat cheese to 1 ounce. No fried foods in either diet.

In the MRFIT trial, a Step I diet with 10 group behavior sessions led by a nutritionist and regular dietary assessment every 1–4 months produced an average LDL-C decrease of 6% without affecting HDL. Caggiula AW, Christakis G, Farrand M et al. The multiple risk factor intervention trial. IV. Intervention on blood lipids. Prevent Med 1981; 10:443–75.

Effect of Various Dietary Fats on Serum Lipids

<table>
<thead>
<tr>
<th>Type of Fat</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saturated FA</td>
<td>Raise</td>
<td>Raise</td>
<td>None</td>
</tr>
<tr>
<td>Trans FA*</td>
<td>Raise</td>
<td>Lower</td>
<td>None</td>
</tr>
<tr>
<td>Polyunsaturated FA*</td>
<td>Lower</td>
<td>Lower</td>
<td>Lower</td>
</tr>
<tr>
<td>Monounsaturated FA*</td>
<td>Lower</td>
<td>Raise</td>
<td>None</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>Raise</td>
<td>Raise</td>
<td>None</td>
</tr>
</tbody>
</table>

* Compared to saturated fat (i.e. effect of substitution)

Monounsaturated fatty acids
- When added to a Step I diet, may further improve LDL-C lowering while returning HDL-C to baseline (i.e. may neutralize the undesirable effect of the Step I diet on HDL-C), even though total fat intake rises to a more palatable 38% of total calories.
- Sources include olive, canola, and peanut oils.

Polyunsaturated fatty acids
- Are a major focus in Step I and II diets.
- When substituted for saturated fats will lower both LDL-C and HDL-C. The overall effect on coronary outcome is not so clear.
- n-6 polyunsaturated FAs (from corn, sunflower, safflower, sesame, and cottonseed oils) increase the risk of gallstones.
- n-3 polyunsaturated FAs (from soybean and canola oil, nuts, mackerel, and salmon) may exert beneficial effects apart from lowering of LDL-C, such as improving arrhythmia thresholds.

Minnesota Coronary Survey
- About 9000 mental health and nursing home inmates were randomized to diets with equal total fat intake (39% of energy).
- Treatment patients received higher polyunsaturated fats (15% v 5%) and lower saturated fats (9% v 18%) than controls.
- Total cholesterol decreased by 14% in treatment patients.
- There were no significant differences in coronary outcomes.

Diet and Reinfarction Trial (DART)
- 2033 male survivors of MI were randomized to: 1) advice to substitute polyunsaturated FAs for saturated FAs; 2) advice to increase fish intake; 3) advice to increase cereal intake; or 4) no advice.
- Subjects assigned to eat more fish showed a 29% reduction in overall mortality which was ascribed to coronary prevention.
- For every 100 patients given advice to eat at least two portions of fatty fish (salmon, trout, mackerel, etc.) per week, nearly four coronary deaths were averted (ARR = 3.7%).

Lyon Diet Heart Study
- This trial assessed the effects of a diet rich in marine and plant n-3 polyunsaturated FA compared to a Step I diet in subjects with a history of MI.

REFERENCES


Comparison of percent fat composition in common oils by saturated (SFA), monounsaturated (MUFA), and polyunsaturated (PUFA) fatty acids:

<table>
<thead>
<tr>
<th>Oil</th>
<th>SFA</th>
<th>MUFA</th>
<th>PUFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coconut</td>
<td>77</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>Butter fat</td>
<td>54</td>
<td>30</td>
<td>12</td>
</tr>
<tr>
<td>Beef fat</td>
<td>51</td>
<td>44</td>
<td>4</td>
</tr>
<tr>
<td>Chicken fat</td>
<td>30</td>
<td>47</td>
<td>22</td>
</tr>
<tr>
<td>Margarine</td>
<td>18</td>
<td>48</td>
<td>29</td>
</tr>
<tr>
<td>Soybean</td>
<td>15</td>
<td>24</td>
<td>61</td>
</tr>
<tr>
<td>Olive</td>
<td>14</td>
<td>77</td>
<td>9</td>
</tr>
<tr>
<td>Corn</td>
<td>13</td>
<td>25</td>
<td>62</td>
</tr>
<tr>
<td>Canola</td>
<td>6</td>
<td>62</td>
<td>31</td>
</tr>
</tbody>
</table>


For every 100 patients randomized to the Mediterranean-type diet, about one fatal coronary event and two non-fatal MIs were averted for every year of treatment. The striking 50% decrease in overall mortality awaits replication in other trials.

Trans fatty acids
- Are created by partial hydrogenation of unsaturated FA in commercial processes designed to solidify vegetable oils.
- Are prominent in margarines and commercial baked goods.
- Have the least desirable effect on plasma lipids by raising LDL-C and lowering HDL-C. They probably also raise lipoprotein (a).
- In an observational study, trans FAs were more strongly associated with coronary events than were other lipid components.8

Summary of dietary principles
- The AHA Step I diet is modestly effective in reducing TC and LDL-C levels.
- The AHA Step II diet may further improve LDL-C at the expense of a lower HDL-C.
- The addition of monounsaturated FAs may improve compliance with the Step I diet without compromising effectiveness and without harming the HDL-C profile.
- Trans FAs should be avoided until their role in coronary disease has been better characterized.
- A Mediterranean-style diet emphasizing plant and marine n-3 fatty acids may prevent coronary events and lower overall mortality. More study is needed to clarify this relationship.
- Diet alone is unlikely to reduce LDL-C levels by more than 10–12% without also reducing HDL-C levels. Substantial lowering of LDL-C requires pharmacologic therapy.

Medical therapy
- Pharmacologic therapy of lipid disorders is now dominated by hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins). They have been conclusively proven to prevent coronary events and save lives in a wide variety of situations and are acceptably safe.
- Alternatives to statins include resins (e.g. cholestyramine), fibrac acid derivatives (e.g. gemfibrozil), and nicotinic acid. They all have a place in lipid management but should be considered as second line agents.

Statins (HMG-CoA reductase inhibitors)
- Competitively inhibit hydroxymethylglutaryl CoA (HMG-CoA) reductase, which catalyzes the rate limiting step in cholesterol synthesis, leading to greater uptake of LDL-C in hepatocytes.
- Decrease LDL-C by a greater amount (30–60%) and have shown a clearer reduction in overall mortality (up to 3.3 lives saved per 100 patients over five years) than the other lipid lowering agents.

8 Hu F, Stampfer MJ, Manson JE et al. Dietary fat intake and the risk of coronary heart disease in women. N Engl J Med 1997;337:1491–9. In this observational study of 80,000 nurses over 14 years, coronary events were 51% higher in those with the highest levels of trans FA intake and 38% lower in those with the highest levels of polyunsaturated FA intake.

Diet Dos
- Bread, cereal, rice, and pasta
- Fresh fruits and vegetables
- Legumes and nuts
- Fish and skinless chicken
- Salmon and mackerel
- Olive and canola oil
- Skim milk and low fat yogurt

Diet Don’ts
- Fried foods
- Red meats
- Dairy products
- Stick margarine
- Many commercial baked goods
Better tolerated than the other three major classes. Roughly 1% of patients taking statin drugs experience reversible, asymptomatic, dose dependent elevations in transaminases to three times normal. Myopathy, defined as creatine phosphokinase elevations to 10 times normal, occurs in <0.2% of patients. Combination therapy with niacin or gemfibrozil increases the risk. Coronary outcomes have been studied in five major randomized placebo controlled trials (see Table 23.1).

The Scandinavian Simvastatin Survival Study (4S)
- In patients with known CAD and high LDL-C (mean 190 mg/dl), simvastatin lowered LDL-C by 38% and increased HDL-C by 8%.
- For every 100 patients treated for five years, simvastatin saved 3.3 lives overall (the greatest benefit ever reported for cholesterol treatment). Coronary events decreased by 42%.

The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study
- In patients with known CAD and moderately elevated LDL-C (mean 150 mg/dl), pravastatin prevented about two coronary deaths and four coronary events for every 100 patients treated for six years.

The Cholesterol and Recurrent Events (CARE) Study
- In patients with a history of MI and normal LDL-C (mean: 139 mg/dl), pravastatin prevented about one coronary death, two non-fatal MIs, one stroke, and four revascularization procedures for every 100 men treated for five years.

The West of Scotland Coronary Prevention Study (WOSCOPS)
- In healthy men with high LDL, pravastatin lowered LDL-C by 26%.
- For every 100 men treated for five years, pravastatin prevented two non-fatal MIs, three revascularizations, and 0.5 coronary death.

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)
- In healthy patients with average total cholesterol (mean 221 mg/dl) and below average HDL-C (mean 36 mg/dl), lovastatin 20–40 mg/day was associated with a 37% reduction in first acute major coronary events over five years.
- All-cause mortality was not affected.

Summary of clinical evidence on statins
- Multiple trials across a broad spectrum of risk demonstrate that aggressive treatment of cholesterol can prevent coronary outcomes and save lives.
- The statin drugs have the most impressive effect on mortality of any lipid lowering agents.

9 Andrade SE, Walker AM, Gottlieb LK et al. Discontinuation of antihyperlipidemic drugs – do rates reported in clinical trials reflect rates in primary care settings? N Engl J Med 1995;332:1125–31. In this retrospective, HMO based cohort study, rates of discontinuation at one year were 46% for niacin, 41% for bile acid sequestrants, 37% for gemfibrozil, and 15% for lovastatin. Discontinuation rates were higher than those reported in randomized trials. Statins are thought to stabilize coronary plaques by mechanisms other than LDL lowering alone: depletion of the plaque's lipid core, strengthening of the fibrous cap, normalization of the endothelium, antiinflammatory effects, and inhibition of thrombus formation.


Although sample sizes were smaller for women in the statin trials, they appeared to experience similar benefits to men. The relative risk reduction in coronary events is consistently about 25–35% regardless of the baseline cholesterol level or type of statin. The absolute risk reduction varies with the subjects. The greatest absolute benefits are seen in patients with highest baseline risk (with CAD and high LDL-C). Absolute risk reductions in overall mortality range from 0 to 3% over five years, depending on the baseline risk. A meta-analysis of 28 trials concluded that the statin drugs reduce the incidence of stroke; diet, fibrates, and resins do not.15

Nicotinic acid (niacin)
- Decreases LDL-C by 10–25% and decreases TG by 20–50%.
- Increases HDL-C by 15–35%.
- Limited by patients’ ability to tolerate the bothersome side effects of cutaneous flushing. Administration of aspirin 30 minutes prior to niacin can reduce flushing.
- Nicotinic acid can cause asymptomatic increases in LFTs, especially at doses ≥3 g/day. LFTs should be monitored every 6–12 weeks in first year, then every six months thereafter.
- Niacin may also cause glucose intolerance, hyperuricemia, and exacerbation of peptic ulcer.
- In the Coronary Drug Project, a secondary prevention study, niacin prevented about four coronary events in every 100 men over six years.16 Coronary mortality was not affected.
- The best tolerated nicotinic acid preparations are once per day agents, such as Niaspan, which may be given at bedtime. In a randomized trial to assess side effects, Niaspan at 2 g per day at bedtime decreased LDL-C by 16% and TGs by 35%, while increasing HDL-C by 26%.17

Bile acid sequestrants (resins)
- Decrease LDL-C by 15–30% and increase HDL-C by 3–5%.
- May increase TG levels. Contraindicated when TG >500 mg/dl.
- Block enterohepatic recirculation of bile acids by binding them in the gut. They do not act systemically.
- Can interfere with absorption; other medications should be taken one hour before or 3–4 hours after the resin.
- May be started with one or two scoops (4–8 g) dissolved in juice 30 minutes before supper, and may be increased as tolerated.
- In healthy men with high LDL-C, cholestyramine prevented two CAD events for every 100 patients treated for seven years. There was no effect on overall mortality.18

Fibrates (gemfibrozil, fenofibrate, clofibrate)
- Increase HDL-C by 10–15% and decrease TG by 20–50%.
- Have only a modest effect on LDL.

Statin trials demonstrate an important axiom of clinical epidemiology: the same relative risk reduction may produce markedly different absolute risk reductions across different patient populations. For example, pravastatin’s 25% RRR in subjects with heart disease (LIPID) saved more than three lives per 100 treated, while its equal 24% RRR in healthy subjects (WOSCOPS) saved less than one life per 100.

15 Bucher HC, Griffith LE, Guyatt GH. Effect of HMG CoA reductase inhibitors on stroke; a meta-analysis of randomized controlled trials. Ann Intern Med 1998;128:89–95. The RRR for stroke was 24% (95% CI, 8–38%).

16 The Coronary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. JAMA 1975;231:360–81. This was the first of five trials of niacin to show statistically significant reductions in coronary events. None of the five studies was sufficiently powered to demonstrate mortality reductions.

17 Goldberg A. Clinical trial experience with extended-release niacin (Niaspan): dose-escalation study. Am J Cardiol 1998;82:35U–8U. In 87 subjects there were no cases of LFTs >3x normal. Nonetheless, 47% of Niaspan patients dropped out compared to 22% of placebo patients. Flushing was noted by 85% but tended to disappear over time.

• Are generally used in patients with low HDL-C or high TGs.
• Are contraindicated in patients with active peptic ulcer or cholelithiasis.
• Should be carefully monitored if used in combination with statin drugs due to the risk of myopathy and rhabdomyolysis.
• In the Helsinki Heart Study, gemfibrozil prevented 1.5 coronary events in 100 patients over five years (RRR=34%) in healthy men with high TC.19 The greatest reduction in coronary events was in patients with the highest triglyceride and lowest HDL-C levels. Total mortality was higher in the gemfibrozil group, mostly due to excess cancer deaths.
• In a more recent trial, gemfibrozil prevented three non-fatal MIs and two coronary deaths over a five year period for every 100 men with coronary artery disease. Average baseline HDL-C and LDL-C were 32 and 112 mg/dl respectively. There was no effect on cancer mortality.20 Interestingly, gemfibrozil’s effect on HDL-C (10% increase) was no better than that achieved by simvastatin at a dose of 40 mg per day (see Table 23.2).

Combination regimens
• Two or even three drugs may be used together.
• In patients with hypercholesterolemia on a maximal-dose statin, niacin or a bile acid sequestrant may be added.
• In patients with hypertriglyceridemia on a fibrate, niacin or a statin may be added.
• The risks of hepatitis, statin induced myopathy, and rhabdomyolysis are increased when niacin and, especially, gemfibrozil are added. Patients on combinations must be monitored closely.

Estrogen
• Decreases LDL-C by 15% and increases HDL-C by 20–30%.
• Can increase TGs. They should be monitored if initially high.
• Case control studies suggest a 40–50% reduction in cardiovascular events; however...
• In postmenopausal women with a history of CAD, treatment with Prempro (estrogen and progesterone) did not lower the overall rates of MI or death from CAD over an average follow up of 4.1 years.21 This occurred despite 10% lowering of LDL-C and 11% raising of HDL-C levels in the estrogen group compared to the placebo group.

Other dyslipidemias

Hypertriglyceridermia
• The role of triglycerides as an independent risk factor for coronary artery disease remains unclear.22
• Triglycerides levels >1000 mg/dl are associated with acute pancreatitis.

HYPERLIPIDEMIA

20 Rubins HB, Rubins SJ, Collins D et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. N Engl J Med 1999;341:410–18. A small randomized crossover trial comparing 3 regimens (nicotinic acid (NIC) at 400 mg tid, lovastatin (LOV) at 20 mg qd, or both) showed the following effects compared to no treatment:

<table>
<thead>
<tr>
<th>TC (%)</th>
<th>LDL (%)</th>
<th>HDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIC</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>LOV</td>
<td>17</td>
<td>25</td>
</tr>
<tr>
<td>NIC+LOV</td>
<td>27</td>
<td>37</td>
</tr>
</tbody>
</table>

No adverse events were reported in this small trial. Vacek JL, Dittmeier G, Chiarelli T, White J, Bell HH. Comparison of lovastatin (20mg) and nicotinic acid (1.2g) with either drug alone for type II hyperlipoproteinemia. Am J Cardiol 1995;76:182–4.
21 Hulley S, Grady D, Bush T et al. Randomized trial of estrogen plus progesterin for secondary prevention of coronary heart disease in postmenopausal women. JAMA 1998; 280:602–13. HERS was the first substantial randomized trial of estrogen replacement therapy for the prevention of heart disease. Previous cohort and case control (i.e. observational) studies had shown 35% to 85% reductions in the risk of coronary events in women taking estrogen replacement.
22 Jeppesen J Hein HO, Saudicani P, Gynelberg E. Triglyceride concentration and ischemic heart disease. An eight-year...
Gemfibrozil, nicotinic acid, and statins are the most effective agents at decreasing triglyceride levels.

**ATP III Classification of Serum Triglycerides (mg/dl)**

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;150</td>
<td>Normal</td>
</tr>
<tr>
<td>150–199</td>
<td>Borderline high</td>
</tr>
<tr>
<td>200–499</td>
<td>High</td>
</tr>
<tr>
<td>&gt;500</td>
<td>Very high</td>
</tr>
</tbody>
</table>

*Treatment of hypertriglyceridemia*

- If triglycerides are >500mg/dl, the level should first be lowered to <500 to prevent pancreatitis. This should be done with a triglyceride lowering drug (fibrate or niacin), and weight loss through very low fat diet and exercise.
- When triglycerides are <500mg/dl, LDL-C lowering therapy becomes the priority.
- In patients with triglycerides >200mg/dl after the LDL-C goal is reached, the sum of LDL+VLDL cholesterol (‘non-HDL cholesterol’) is a secondary target. A goal of non-HDL cholesterol 30mg/dl higher than the LDL-C goal should be sought.

**Non-HDL Cholesterol Targets for Patients with Triglycerides >200mg/dl After Attaining LDL Goal**

<table>
<thead>
<tr>
<th>Level</th>
<th>LDL-C goal (mg/dl)</th>
<th>Non-HDL-C goal (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAD or equivalent</td>
<td>&lt;100</td>
<td>&lt;130</td>
</tr>
<tr>
<td>2 or more risk factors</td>
<td>&lt;130</td>
<td>&lt;160</td>
</tr>
<tr>
<td>0 or 1 risk factor</td>
<td>&lt;100</td>
<td>&lt;130</td>
</tr>
</tbody>
</table>

*Low HDL-C (<40mg/dl)*

- Independently associated with coronary events. Low HDL-C increases risk even when total cholesterol is <200mg/dl.
- Every 1 mg/dl decrease in HDL-C is associated with a 2–3% increased risk of coronary events.
- Levels are decreased by cigarette smoking, sedentary lifestyle, obesity, β blockers, and anabolic steroids.
- Levels are increased by moderate alcohol use, exercise, and weight reduction.
- Statins, fibric acid derivatives, and niacin all increase HDL-C, with the greatest effects (20–30% increase) produced by niacin.

*Treatment*

- First reach LDL goal
- Weight loss through diet and exercise.
- If triglycerides are 200–499 mg/dl, achieve non-HDL-C goal.
- If triglycerides are <200mg/dl (isolated low HDL-C), in a patient with CAD or equivalent, consider nicotinic acid or fibrate.
Table 23.1 Summary of major trials of statin drugs.

<table>
<thead>
<tr>
<th>Study name</th>
<th>Type of prevention</th>
<th>Baseline LDL-C (avg)</th>
<th>Active treatment</th>
<th>Effect on LDL-C(%)</th>
<th>Mortality RRR(%)</th>
<th>ARR(%)</th>
<th>CHD events RRR(%)</th>
<th>ARR(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S</td>
<td>Secondary</td>
<td>188 mg/dl</td>
<td>Simvastatin</td>
<td>−38</td>
<td>30</td>
<td>3.2</td>
<td>34</td>
<td>8.2</td>
</tr>
<tr>
<td>LIPID</td>
<td>Secondary</td>
<td>150 mg/dl</td>
<td>Pravastatin</td>
<td>−25</td>
<td>22</td>
<td>3.1</td>
<td>24</td>
<td>3.6</td>
</tr>
<tr>
<td>CARE</td>
<td>Secondary</td>
<td>139 mg/dl</td>
<td>Pravastatin</td>
<td>−28</td>
<td>20</td>
<td>0.8</td>
<td>24</td>
<td>3.0</td>
</tr>
<tr>
<td>WOSCOP</td>
<td>Primary</td>
<td>192 mg/dl</td>
<td>Pravastatin</td>
<td>−26</td>
<td>28</td>
<td>0.9</td>
<td>31</td>
<td>2.4</td>
</tr>
<tr>
<td>AFCAP</td>
<td>Primary</td>
<td>150 mg/dl</td>
<td>Lovastatin</td>
<td>−25</td>
<td>NS</td>
<td>NS</td>
<td>40</td>
<td>2.3</td>
</tr>
</tbody>
</table>

CHD events = CHD deaths plus non-fatal MIs

Table 23.2 Lipid lowering effects (%) of selected statin drugs.

<table>
<thead>
<tr>
<th>Agent (dose in mg)</th>
<th>TC</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin (80)</td>
<td>−42</td>
<td>−54</td>
<td>+0</td>
<td>−25</td>
</tr>
<tr>
<td>Atorvastatin (40)</td>
<td>−40</td>
<td>−51</td>
<td>+5</td>
<td>−32</td>
</tr>
<tr>
<td>Simvastatin (80)*</td>
<td>−35</td>
<td>−47</td>
<td>+8</td>
<td>−23</td>
</tr>
<tr>
<td>Simvastatin (40)</td>
<td>−30</td>
<td>−41</td>
<td>+10</td>
<td>−15</td>
</tr>
<tr>
<td>Pravastatin (40)</td>
<td>−24</td>
<td>−34</td>
<td>+6</td>
<td>−10</td>
</tr>
<tr>
<td>Lovastatin (40)</td>
<td>−23</td>
<td>−31</td>
<td>+5</td>
<td>−2</td>
</tr>
<tr>
<td>Fluvastatin (40)</td>
<td>−19</td>
<td>−23</td>
<td>−3</td>
<td>−13</td>
</tr>
</tbody>
</table>

*The 80 mg dose was not studied in the CURVES study. The 80 mg figures were taken from Davidson MH, Stein EA, Dujovne CA et al. The efficacy and six-week tolerability of simvastain 80 and 160 mg/day. Am J Cardiol 1997;79:38–42. This study was funded by the makers of simvastatin.

Table 23.3 Agents for hyperlipidemia.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage form</th>
<th>Dosage range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Statins</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin (Lipitor)</td>
<td>10, 20, 40 mg</td>
<td>10–40 mg PO qd (any time of day)</td>
</tr>
<tr>
<td>Lovastatin (Mevacor)</td>
<td>10, 20, 40 mg</td>
<td>10–80 mg PO q evening</td>
</tr>
<tr>
<td>Fluvastatin (Lescol)</td>
<td>20, 40 mg</td>
<td>20–40 mg PO q evening</td>
</tr>
<tr>
<td>Pravastatin (Pravachol)</td>
<td>10, 20, 40 mg</td>
<td>10–40 mg q evening</td>
</tr>
<tr>
<td>Simvastatin (Zocor)</td>
<td>5, 10, 20, 40, 80 mg</td>
<td>5–80 mg PO q evening</td>
</tr>
<tr>
<td>Cerivastatin (Baycol)</td>
<td>0.2, 0.3, 0.4 mg</td>
<td>0.3–0.8 mg PO q evening</td>
</tr>
<tr>
<td><strong>Fibrates</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gemfibrozil (Lopid)</td>
<td>600 mg</td>
<td>600 mg PO bid before meals</td>
</tr>
<tr>
<td>Fenoﬁbrate (Tricor)</td>
<td>67 mg</td>
<td>201 mg qd</td>
</tr>
<tr>
<td>Colestipol (Colestid)</td>
<td>1 packet = 5 g</td>
<td>5 mg qd–15 mg bid</td>
</tr>
<tr>
<td><strong>Bile acid sequestrants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholestyramine (Questran)</td>
<td>4 g packets</td>
<td>4–12 g in 8 oz H2O PO bid</td>
</tr>
<tr>
<td><strong>Niacin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niacin (nicotinic acid) (Nicolar)</td>
<td>500 mg</td>
<td>1–2 g PO tid with food</td>
</tr>
<tr>
<td><strong>Female hormones</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjugated estrogens (Premarin)</td>
<td>0.625 mg</td>
<td>0.625 mg PO qd</td>
</tr>
</tbody>
</table>
### Table 23.4  Estimated ten-year risk of myocardial infarction in men. (Framingham point scores)*

<table>
<thead>
<tr>
<th>Age</th>
<th>Points</th>
<th>HDL</th>
<th>Points</th>
<th>Points if untreated</th>
<th>Points if treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–34</td>
<td>-9</td>
<td>≥60</td>
<td>-1</td>
<td>&lt;120</td>
<td>0</td>
</tr>
<tr>
<td>35–39</td>
<td>-4</td>
<td>50–59</td>
<td>0</td>
<td>120–129</td>
<td>0</td>
</tr>
<tr>
<td>40–44</td>
<td>0</td>
<td>40–49</td>
<td>1</td>
<td>130–139</td>
<td>1</td>
</tr>
<tr>
<td>45–49</td>
<td>3</td>
<td>&lt;40</td>
<td>2</td>
<td>140–159</td>
<td>1</td>
</tr>
<tr>
<td>50–54</td>
<td>6</td>
<td></td>
<td>≥160</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>55–59</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60–64</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65–69</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70–74</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75–79</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cholesterol</td>
<td>Points at 20–39</td>
<td>Points at 40–49</td>
<td>Points at 50–59</td>
<td>Points at 60–69</td>
<td>Points at 70–79</td>
</tr>
<tr>
<td>&lt;160</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>160–199</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>200–239</td>
<td>7</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>240–279</td>
<td>9</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>&gt;280</td>
<td>11</td>
<td>8</td>
<td>5</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Smoker</td>
<td>8</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>1</td>
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</table>

<table>
<thead>
<tr>
<th>Point total</th>
<th>10-year risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0</td>
<td>&lt;1</td>
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<tr>
<td>0–4</td>
<td>1</td>
</tr>
<tr>
<td>5–6</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>4</td>
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<tr>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>12</td>
<td>10</td>
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<tr>
<td>13</td>
<td>12</td>
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<tr>
<td>14</td>
<td>16</td>
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<tr>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>16</td>
<td>25</td>
</tr>
<tr>
<td>≥1</td>
<td>≥30</td>
</tr>
</tbody>
</table>

*Total points = age + total cholesterol + smoking + HDL + blood pressure
Table 23.5  Estimated ten-year risk of myocardial infarction in women.*

<table>
<thead>
<tr>
<th>Age</th>
<th>Points</th>
<th>HDL</th>
<th>Points</th>
<th>Systolic BP</th>
<th>Points if untreated</th>
<th>Points if treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–34</td>
<td>−7</td>
<td>≥60</td>
<td>−1</td>
<td>&lt;120</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>35–39</td>
<td>−3</td>
<td>50–59</td>
<td>0</td>
<td>120–129</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>40–44</td>
<td>0</td>
<td>40–49</td>
<td>1</td>
<td>130–139</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>45–49</td>
<td>3</td>
<td>&lt;40</td>
<td>2</td>
<td>140–159</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>50–54</td>
<td>6</td>
<td></td>
<td>≥160</td>
<td></td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>55–59</td>
<td>8</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>60–64</td>
<td>10</td>
<td></td>
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<tr>
<td>65–69</td>
<td>12</td>
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<tr>
<td>70–74</td>
<td>14</td>
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<td></td>
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<tr>
<td>75–79</td>
<td>16</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Total cholesterol</th>
<th>Points at 20–39</th>
<th>Points at 40–49</th>
<th>Points at 50–59</th>
<th>Points at 60–69</th>
<th>Points at 70–79</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;160</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>160–199</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>200–239</td>
<td>8</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>240–279</td>
<td>11</td>
<td>8</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>&gt;280</td>
<td>13</td>
<td>10</td>
<td>7</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Smoking</th>
<th>Points at 20–39</th>
<th>Points at 40–49</th>
<th>Points at 50–59</th>
<th>Points at 60–69</th>
<th>Points at 70–79</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-smoker</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Smoker</td>
<td>9</td>
<td>7</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

**Point total  10-year risk (%)**

<table>
<thead>
<tr>
<th>Points</th>
<th>Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;9</td>
<td>&lt;1</td>
</tr>
<tr>
<td>9–12</td>
<td>1</td>
</tr>
<tr>
<td>13–14</td>
<td>2</td>
</tr>
<tr>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>18</td>
<td>6</td>
</tr>
<tr>
<td>19</td>
<td>8</td>
</tr>
<tr>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>22</td>
<td>17</td>
</tr>
<tr>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>24</td>
<td>27</td>
</tr>
<tr>
<td>≥25</td>
<td>≥30</td>
</tr>
</tbody>
</table>

*Total points = age + total cholesterol + smoking + HDL + blood pressure
24 Hypertension
Michael Tanner

Epidemiology
Prevalence and burden of hypertension
- Over 50 million Americans have blood pressures over 140/90 or are taking antihypertensive medications.¹
- Hypertension is a leading risk factor for coronary artery disease (CAD), stroke, heart failure, aortic aneurysm, renal failure, left ventricular hypertrophy, and retinopathy.
- From 1972 to 1994, the age adjusted mortality rate from CAD fell by 53% and that from stroke by 60%.¹ Improved detection and treatment of hypertension have contributed to these amazing declines in mortality.

Prevalence (%) of Hypertension by Age and Sex, 1988–91²

<table>
<thead>
<tr>
<th>Age</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–34</td>
<td>9.2</td>
<td>3.0</td>
</tr>
<tr>
<td>35–44</td>
<td>20.0</td>
<td>12.3</td>
</tr>
<tr>
<td>45–54</td>
<td>35.7</td>
<td>23.2</td>
</tr>
<tr>
<td>55–64</td>
<td>48.7</td>
<td>46.5</td>
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<tr>
<td>65–74</td>
<td>59.0</td>
<td>57.8</td>
</tr>
<tr>
<td>≥75</td>
<td>63.7</td>
<td>75.2</td>
</tr>
</tbody>
</table>

Prevalence (%) of Hypertension in Adults 20 and Older by Race and Sex, 2000²

<table>
<thead>
<tr>
<th>Race</th>
<th>African American</th>
<th>Hispanic</th>
<th>White</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>36.7</td>
<td>24.2</td>
<td>25.2</td>
</tr>
<tr>
<td>Women</td>
<td>36.6</td>
<td>22.4</td>
<td>20.5</td>
</tr>
</tbody>
</table>

Diagnosis
History
- Age at onset, duration, and severity
- Other medical problems that could affect the choice of an agent: diabetes, CAD, heart failure, asthma, renal failure, etc.
- Side effects of any previous treatment
- Medications and substances that can raise blood pressure:
  - erythropoietin
  - oral contraceptives
  - steroids
  - appetite suppressants.
Note: the nasal decongestant pseudoephedrine (Sudafed) did not raise blood pressure in a placebo controlled crossover trial.³
- Cardiovascular disease risks: smoking, cholesterol, diabetes, family history of early MI or sudden death

Physical exam
- Weight
- Fundi for hemorrhages, exudates, papilledema
- Evidence of vascular disease (for example, bruits)
- Abdomen for subxiphoid or mid-line bruises, aortic pulsation
- Extremities for evidence of coarctation (asymmetry in blood pressure, brachial-femoral pulse delay)


- Coronary artery disease is the leading cause of death in the United States, accounting for 466,000 deaths in 1997.
- Stroke, the third leading cause of death, caused 160,000 deaths in 1997.

3 Coates ML, Rembold CM, Farr BM. Does pseudoephedrine increase blood pressure in patients with controlled hypertension? J Fam Pract 1993; 40:22–6. Pseudoephedrine 60 mg PO qid given for one week did not raise blood pressure in this trial of 25 adults with medically controlled hypertension.
Blood Pressure Cuff Technique

- A cuff that is too small can artificially raise the reading, harming specificity.
- The patient’s arm should be at heart level and supported.
- The cuff should be inflated to 200 mmHg (20–30 above systolic for subsequent readings) and deflated at 3 mmHg per heartbeat.
- Systolic pressure is measured at the first appearance of clear, repetitive tapping sounds. Obtaining systolic pressure by radial artery palpation can clarify ambiguous readings.
- Diastolic pressure is measured at the disappearance of repetitive sounds. Determining diastolic pressure requires a stethoscope.
- To recognize postural hypotension, the pressure should be taken immediately and 1–5 minutes after standing.

JNC-6 Classification of Blood Pressure

<table>
<thead>
<tr>
<th></th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal</td>
<td>&lt; 120</td>
<td>&lt; 80</td>
</tr>
<tr>
<td>Normal</td>
<td>&lt; 130</td>
<td>&lt; 85</td>
</tr>
<tr>
<td>High-normal</td>
<td>130–139</td>
<td>85–89</td>
</tr>
<tr>
<td>Stage 1 (mild)</td>
<td>140–159</td>
<td>90–99</td>
</tr>
<tr>
<td>Stage 2 (moderate)</td>
<td>160–179</td>
<td>100–109</td>
</tr>
<tr>
<td>Stage 3 (severe)</td>
<td>≥ 180</td>
<td>≥ 110</td>
</tr>
</tbody>
</table>

- When systolic and diastolic pressures fall into different categories, the higher stage rules.
- To avoid mislabeling patients who may have only transient, anxiety related, “white coat” hypertension, three high readings at least a week apart are necessary for diagnosis. Stage 2 or 3 hypertension is rarely caused by anxiety alone.

Initial diagnostic tests

- Electrolytes: glucose, creatinine, potassium, uric acid
- Lipid profile
- Urinalysis
- Urinary albumin/creatinine ratio for microalbuminuria in diabetic patients
- Electrocardiogram (for left ventricular hypertrophy by voltage criteria or evidence of CAD)

Treatment

Is treatment effective?

- In severe hypertension, dramatically so. In the 1967 Veterans’ Administration Study\(^5\) of males with severe hypertension (115–129 diastolic), severe morbidity or mortality occurred within two years in 27 of 70 control patients compared with two of 73 treated patients (RRR = .93, ARR = .36, NNT = 3).
- The benefits of treating mild hypertension are much less pronounced. In the MRC trial\(^6\) of mild hypertensives


(90–109 mmHg diastolic), 850 patients needed to be treated for one year in order to prevent one stroke.

- At all levels of hypertension, the reduction in stroke gained by treatment is greater than the reduction in MI.7

Lifestyle Modification

- Weight reduction by diet and exercise. The Trials of Hypertension Prevention8 randomized 1191 normotensive, overweight patients aged 30–54 to a weight loss or usual care group. After three years, the patients were analyzed by quintiles.

<table>
<thead>
<tr>
<th>Mean weight change</th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>−8.8 kg (quintile 1)</td>
<td>−5.0</td>
<td>−7.0</td>
</tr>
<tr>
<td>+7.3 kg (quintile 5)</td>
<td>+2.5</td>
<td>−0.7</td>
</tr>
</tbody>
</table>

- In clinical trials, sodium restriction in hypertensive patients reduces systolic blood pressure by 2.5–4.8 mmHg and diastolic by 1.1–1.9 mmHg.9

- Alcohol should be limited to a maximum of two drinks a day.

- Adequate intake of potassium, magnesium, and calcium is recommended.

When lifestyle modification fails: principles of pharmacological therapy

- Identify any coexisting medical problems and select an appropriate agent. β Blockers and diuretics are the first line agents in uncomplicated hypertension.

- Once a day dosing to maximize compliance.10

- The dose of one drug, if well tolerated, should be maximized before starting the next; this strategy minimizes drug interactions. Alternatively, an agent from another class may be added to a less than maximal dose of the initial drug; this strategy minimizes dose dependent side effects.

- Because of synergy, thiazide diuretics make ideal second agents if not used initially.

- Use the minimum number of drugs at the minimum doses necessary to attain the target blood pressure.

JNC-6 Blood Pressure Targets

Most patients 140/90
Diabetes, heart failure, renal failure 130/85
Isolated systolic hypertension of the elderly 140/90
- If 140/90 is unattainable... Systolic < 160
Proteinuria > 1 gram per day 125/75

- The Hypertension Optimal Treatment trial11 randomized 18,790 patients with an average initial blood pressure of 170/105 to target diastolic blood pressures of ≤90, ≤85, or ≤80 mmHg. The lowest incidence of major cardiovascular events occurred at a mean achieved diastolic blood pressure of 82.6 mmHg.


Reduction in DBP Stroke CAD
5 mmHg −34% −21%
7.5 mmHg −46% −29%
10 mmHg −56% −37%


Determining the exact degree to which alcohol raises blood pressure is difficult, due to the ethical unfeasibility of doing a controlled trial and patients’ tendency to underreport alcohol consumption.


Except at very high blood pressure levels, hypertension is asymptomatic. Patients taking antihypertensive drugs should be told that feeling OK is not an indication to skip doses.


Hyperaldosteronism, hypercortisolism, hyperparathyroidism, acromegaly, pheochromocytoma, and coarctation of the aorta taken together probably account for <1% of hypertension cases.
Resistant or severe hypertension
Hypertension is termed resistant when a compliant patient fails three drugs (including a diuretic) at maximal doses. Secondary causes of hypertension should be reconsidered.

Secondary hypertension
- There are no population data on the true prevalence of secondary hypertension; it is estimated to be present in roughly 5% of cases.
- The most common cause of secondary hypertension is renal artery stenosis secondary to fibromuscular dysplasia (in young women) or atherosclerosis.
- Factors that suggest renovascular hypertension include:
  —onset at <20 or >50 years
  —abdominal bruit
  —grade 3 or 4 retinopathy
  —renal failure, especially if induced by an ACE inhibitor
  —asymmetry of kidney size by ultrasound.

Renal artery stenosis
- The non-invasive imaging techniques for diagnosing renal artery stenosis have good or excellent sensitivity and specificity compared to standard angiography, the invasive gold standard.
  —Magnetic resonance angiography with gadolinium
  —Nuclear renal scan
  —Duplex ultrasound
  —Spiral CT angiography with contrast dye.
- The real question is how much the therapy (PTRA) helps in lowering blood pressure.
  —Renal artery balloon angioplasty rarely cures hypertension.\textsuperscript{13} Despite undergoing the procedure, the great majority of patients need to continue taking antihypertensive drugs.
  —Restenosis limits the benefits of renal artery angioplasty, particularly in ostial lesions.\textsuperscript{14} Stenting improves the restenosis rate.
  —Because of its high cost, risk, and limited efficacy, renal artery angioplasty should be reserved for patients who are failing medical management: inability to attain target blood pressure despite taking three or more antihypertensive drugs at maximal doses.

Minoxidil
- Indicated for resistant hypertension that is very severe or associated with target organ damage.
- Because it is a direct acting peripheral vasodilator, minoxidil causes increased cardiac rate and output, and salt and water retention. These effects can be lessened by coadministration of a loop diuretic and \( H \) blocker. Minoxidil should not be given alone.

\textsuperscript{12} The sensitivity of scintigraphy is increased by the administration of captopril 50 mg PO one hour prior to the test. Captopril renograms are 89% sensitive and 92% specific (\(+ LR = 11, - LR = 0.12\)). Blaufox MD, Bongiovanni J, Davis BR. Cost efficacy of the diagnosis and therapy of renovascular hypertension. J Nucl Med 1996;37:171–7.


\textsuperscript{14} Van de Ven PJ, Kaa toe R, Beutler IJ et al. Arterial stenting and balloon angioplasty in ostial atherosclerotic renovascular disease: a randomized trial. Lancet 1999;353:282–6. At six months, the primary patency rate was 29% for standard angioplasty and 75% for angioplasty with stenting.
Hypertensive crises

- A hypertensive emergency requires intravenous therapy in a monitored setting for immediate lowering of blood pressure to prevent further end organ damage. Examples include pre-eclampsia, intracranial hemorrhage, heart failure with pulmonary edema, dissecting aortic aneurysm, unstable angina, and hypertensive encephalopathy.
- In a hypertensive urgency, the patient is asymptomatic. Blood pressure can be lowered over a period of hours with oral medications. The patient should be seen the following day.
- Therapy recommendations are not evidence based because of the difficulties inherent in designing a randomized controlled trial.
- Hypertensive urgencies can be managed with oral β blockers, ACE inhibitors, α blockers, or calcium channel blockers. Diuretics are not first line agents because very high blood pressure may increase sodium excretion.
- Many patients presenting with a hypertensive urgency are non-compliant with their prescribed medications. Therapy often consists of saying: “Take your pills”.
- The risks of overly aggressive intervention (myocardial, cerebrovascular, and renal hypoperfusion) must be considered. Mean arterial blood pressure (MAP) should be reduced by ≤25% within minutes to two hours, then toward 160/100 (MAP 120).

Notes on the agents

Thiazide diuretics

- Low dose thiazide diuretics are the first line drugs in uncomplicated hypertension because they have been shown to reduce cardiovascular events and mortality in the setting of hypertension, as compared with no treatment.
- First line agents in African Americans, whose hypertension tends to be characterized by low renin, expanded blood volume, and sensitivity to salt.
- First line agents in isolated systolic hypertension of elderly patients.
- Low dose diuretics may be used in diabetes.
- Diuretics are ideal second agents if not used first because of synergy with the other drug classes.
- Hydrochlorothiazide performed better than drugs from five other classes in a one-year study of left ventricular hypertrophy reduction.
- Hydrochlorothiazide and chlorthalidone are incredibly cheap (a penny per pill).
- Thiazides prevent recurrence of calcium oxalate renal stones.
- Loop diuretics (furosemide, ethacrynic acid, amiloride) are not indicated in the treatment of uncomplicated hypertension. They should be reserved for fluid overloaded patients

19 SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA 1991;265:3255–64. In this study of 4736 people aged 60 and older, stepped care treatment with low dose chlorthalidone as the first drug prevented three strokes per 100 persons treated for five years, compared to placebo.
with serious illness (heart failure, renal failure, cirrhosis) in whom gentler diuretics have failed.
- Gout, but not asymptomatic hyperuricemia, is a relative contraindication to thiazides because of their tendency to raise uric acid levels.
- Thiazide diuretics are inefficacious in patients with creatinine \( \geq 2.5 \text{ mg/dl} \).

**β Blockers**
- Reduce the incidence of stroke and heart failure in hypertensive patients. Along with diuretics, they are first line agents in uncomplicated hypertension.
- In the post-MI setting, β blockers decrease the rate of sudden death, overall mortality, and recurrent infarction. A history of MI with preserved ventricular function is one of the strongest indications for a β blocker. See Chapter 10 for a full discussion.
- In diabetic patients taking insulin, the dangerous ability of β blockers to mask the symptoms of hypoglycemia must be weighed against their beneficial effects on CAD, which is by far the most common cause of death in these patients.
- Relatively contraindicated in asthma because of their bronchospastic effects.

**Angiotensin converting enzyme inhibitors**
- First line agents in diabetes, heart failure, and renal insufficiency. (See the related chapters for a full discussion.)
- Ramipril prevented deaths, MI, and stroke in the HOPE trial, which randomized 9255 patients \( \geq 55 \) years old with established CAD or diabetes plus \( \geq 1 \) cardiac risk factor. The study suggested a greater role for ACE inhibitors in the therapy of CAD with preserved ventricular function.
- ACE inhibitors must be used with caution in the setting of renal failure because they can accelerate rather than retard the process, particularly at higher creatinine levels.
- A marked increase in creatinine in a patient with renal insufficiency taking an ACE inhibitor suggests renal artery stenosis. Bilateral renal artery stenosis is an absolute contraindication to ACE inhibition.

**Calcium channel blockers**
- The dihydropyridine calcium blockers act as vasodilators. Diltiazem and verapamil are non-dihydropyridines; they slow AV conduction and decrease contractility.
- Short acting calcium channel blockers, particularly nifedipine, should not be used because of observational studies and randomized controlled trials suggesting they increase the risk of myocardial infarction in hypertensive patients.
- The Appropriate Blood Pressure Control in Diabetes (ABCD) trial found that the dihydropyridine nisoldipine


was associated with a higher incidence of MI in hypertensives with diabetes compared with the ACE inhibitor enalapril (RR = 9.5).  

- The Syst-Eur trial found that nitrrendipine (a dihydropyridine not available in the US) was associated with a 42% reduction in stroke over two years in elderly patients. Based on this, JNC-6 recommended dihydropyridines as second line agents (after thiazide diuretics) in elderly people.

**α Blockers**

- The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) is a randomized, double blind, active controlled trial sponsored by the National Heart, Lung, and Blood Institute. The ongoing study was designed to compare the effects of antihypertensive treatment on CAD with chlorthalidone (a thiazide diuretic), amlodipine, lisinopril, and doxazocin (an α blocker). In early 2000, an ALLHAT data review committee discontinued the doxazocin treatment arm when it became clear that doxazocin is inferior to chlorthalidone in preventing cardiovascular disease, especially heart failure. The relative risk of heart failure at four years was 2.04 in the doxazocin group as compared with the chlorthalidone group.

**Angiotensin II antagonists**

- Do not potentiate bradykinin; therefore, they do not cause the dry cough seen in 10% of patients who take ACE inhibitors.
- Long term studies are necessary to see if the angiotensin receptor blockers are comparable to ACE inhibitors in their ability to slow the progression of diabetic and non-diabetic nephropathy.

---


Dihydropyridine calcium channel blockers: amlodipine, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nitrendipine


ALLHAT results suggest that α blockers may be harmful through promotion of fluid retention.
Table 24.1 Choosing the right antihypertensive drug in patients with other medical conditions.

<table>
<thead>
<tr>
<th>Clinical situation</th>
<th>Preferred</th>
<th>Requires special monitoring</th>
<th>Relatively or absolutely contraindicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>African-Americans</td>
<td>Diuretics</td>
<td></td>
<td>β Blockers</td>
</tr>
<tr>
<td>Asthma/COPD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>β Blockers</td>
<td>Direct vasodilators</td>
<td>Short acting calcium blockers</td>
</tr>
<tr>
<td></td>
<td>ACE inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Calcium blockers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine &gt; 2.5 mg/dl</td>
<td>Loop diuretics</td>
<td>ACE inhibitors</td>
<td>Thiazide diuretics</td>
</tr>
<tr>
<td></td>
<td>ACE inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>ACE inhibitors</td>
<td>β Blockers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low dose diuretics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophageal varices</td>
<td>β Blockers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gout</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure (systolic)</td>
<td>ACE inhibitors</td>
<td>β Blockers</td>
<td>Calcium blockers</td>
</tr>
<tr>
<td></td>
<td>Diuretics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated systolic hypertension of the elderly</td>
<td>Diuretics</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dihydropyridines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney stones – calcium</td>
<td>Thiazide diuretics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>Diuretics</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ACE inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraine headaches</td>
<td>β Blockers</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Calcium blockers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Methyldopa</td>
<td></td>
<td>ACE inhibitors, angiotensin receptor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>blockers (2nd and 3rd trimesters only)</td>
</tr>
<tr>
<td></td>
<td>α Blockers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostatic hypertrophy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncomplicated</td>
<td>Diuretics</td>
<td></td>
<td>β Blockers</td>
</tr>
</tbody>
</table>
Table 24.2 Selected agents for hypertension.

<table>
<thead>
<tr>
<th>Type of drug</th>
<th>Dosage forms (mg)</th>
<th>Usual dosage</th>
<th>Major adverse effects, comments on the drug classes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACE inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril (Capoten)</td>
<td>12.5/25/50/100</td>
<td>6.25–75 bid</td>
<td>Hyperkalemia, especially in diabetic patients</td>
</tr>
<tr>
<td>Enalapril (Vasotec)</td>
<td>2.5/5/10/20</td>
<td>2.5–40 qd</td>
<td>Dry cough in roughly 10% of patients</td>
</tr>
<tr>
<td>Lisinopril (Prinivil, Zestril)</td>
<td>5/10/20/40</td>
<td>5–40 qd</td>
<td>Contraindicated in bilateral renal artery stenosis and 2nd and 3rd trimesters of pregnancy</td>
</tr>
<tr>
<td>Ramipril (Altace)</td>
<td>1.25/2.5/5/10</td>
<td>1.25–10 qd</td>
<td></td>
</tr>
<tr>
<td><strong>β Blockers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atenolol (Tenormin)</td>
<td>25/50/100</td>
<td>25–100 qd</td>
<td>Bronchospasm, bradycardia, heart failure; may mask hypoglycemia in diabetic patients, especially those taking insulin</td>
</tr>
<tr>
<td>Metoprolol (Lopressor)</td>
<td>50/100</td>
<td>50–200 qd</td>
<td></td>
</tr>
<tr>
<td>Propranolol (Inderal)</td>
<td>10/20/40/60/80</td>
<td>20–120 bid</td>
<td></td>
</tr>
<tr>
<td><strong>Calcium channel blockers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nifedipine (Procardia XL)</td>
<td>30/60/90</td>
<td>30–90 qd</td>
<td>Dihydropyridines: edema, headache</td>
</tr>
<tr>
<td>Diltiazem (Tiazac)</td>
<td>120/180/240/300/360</td>
<td>120–360 qd</td>
<td>Diltiazem and verapamil: AV block, worsening of systolic dysfunction</td>
</tr>
<tr>
<td>Verapamil (Calan, Isoptin)</td>
<td>40/80/120</td>
<td>40–240 bid</td>
<td></td>
</tr>
<tr>
<td>Amlodipine (Norvasc)</td>
<td>2.5/5/10</td>
<td>2.5–10 qd</td>
<td></td>
</tr>
<tr>
<td><strong>Diuretics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Thiazide</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorthalidone (Hygroton)</td>
<td>25/50/100</td>
<td>12.5–50 qd</td>
<td>Hypokalemia, dyspepsia, fatigue, dizziness</td>
</tr>
<tr>
<td>Hydrochlorothiazide (HCTZ) (Esidrix)</td>
<td>25/50/100</td>
<td>12.5–50 qd</td>
<td></td>
</tr>
<tr>
<td><strong>Loop</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethacrynic acid (Edecrin)</td>
<td>25/50</td>
<td>12.5–50 bid</td>
<td>Hypokalemia</td>
</tr>
<tr>
<td>Furosemide (Lasix)</td>
<td>20/40/80</td>
<td>10–160 bid</td>
<td>Azotemia</td>
</tr>
<tr>
<td><strong>Potassium sparing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spironolactone (Aldactone)</td>
<td>25/50/100</td>
<td>12.5–50 bid</td>
<td>Hyperkalemia</td>
</tr>
<tr>
<td>Triamterene (Dyrenium)</td>
<td>50/100</td>
<td>50–150 qd</td>
<td></td>
</tr>
<tr>
<td>Category</td>
<td>Drug</td>
<td>Dose</td>
<td>Frequency</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>---------------</td>
<td>---------------</td>
<td>-----------</td>
</tr>
<tr>
<td><strong>α Blockers</strong></td>
<td>Prazocin (Minipress)</td>
<td>0.5/5</td>
<td>1–10 bid</td>
</tr>
<tr>
<td></td>
<td>Terazocin (Hytrin)</td>
<td>0.5/5/10</td>
<td>1–10 bid</td>
</tr>
<tr>
<td><strong>α, β Blockers</strong></td>
<td>Labetalol (Normodyne)</td>
<td>100/200/300</td>
<td>100–600 bid</td>
</tr>
<tr>
<td><strong>α₂ Agonists</strong></td>
<td>Clonidine (Catapres)</td>
<td>0.1/0.2/0.3</td>
<td>0.1–0.6 bid</td>
</tr>
<tr>
<td></td>
<td>Methyldopa (Aldomet)</td>
<td>125/250/500</td>
<td>125–1000 bid</td>
</tr>
<tr>
<td><strong>Direct vasodilators</strong></td>
<td>Hydralazine (Apresoline)</td>
<td>10/25/50/100</td>
<td>25–150 bid</td>
</tr>
<tr>
<td></td>
<td>Minoxidil (Loniten)</td>
<td>2.5/10</td>
<td>2.5 qd-40 bid</td>
</tr>
<tr>
<td><strong>Angiotensin receptor blockers</strong></td>
<td>Losartan (Cozaar)</td>
<td>25/50/100</td>
<td>25–100</td>
</tr>
</tbody>
</table>
Epidemiology

- The prevalence of irritable bowel syndrome (IBS) is difficult to ascertain given the lack of diagnostic certainty. IBS may be present in 5–25% of all adults, with a predominance of women and young people (<45).\(^1\)
- Patients with IBS utilize the healthcare system frequently and account for up to 12% of visits to general practitioners.\(^2\)
- While there is no increased mortality with IBS, there is significant morbidity in terms of pain, discomfort, and days lost from work.

Pathophysiology

- IBS patients experience abdominal pain at low intestinal gas volumes that are usually not painful to, or even noticed by, controls. This altered perception appears to be mediated by serotonin as part of the “brain–gut” axis.\(^3\)
- Patients with IBS have altered bowel motility in the intestine compared to control subjects and are more sensitive to this contractile activity.\(^4\)
- In IBS, colonic motility is affected by emotion – increased with anger and pain, decreased with crying.\(^5\)
- IBS may represent a generalized disorder of smooth muscle and its innervation, not simply an intestinal disease.\(^6\)

Diagnosis

Traditionally, IBS has been a diagnosis of exclusion. There is a trend toward making the diagnosis with a judicious approach designed to exclude a small number of more serious disorders.

Rome II criteria for diagnosis of IBS\(^7\)

- At least 12 weeks – not necessarily consecutive – within the past year of abdominal pain or discomfort that is characterized by at least two of the following features:
  - onset associated with a change in frequency of stool
  - onset associated with a change in form (appearance) of stool
  - relief with defecation.

Intestinal symptoms

- Abdominal pain tends to be crampy or bloating.
- Abnormal stool form and frequency can take the form of predominantly diarrhea, predominantly constipation, or alternating diarrhea and constipation.
- Tenesmus, straining, sense of incomplete evacuation.

The CDC and NHANES do not have data on IBS prevalence.


Passage of mucus per rectum.
- Physical exam is normal, except for mild abdominal tenderness.
- Laboratory and radiologic studies are normal.

**Extraintestinal symptoms**
- Gastroesophageal reflux, globus sensation, and esophageal dysfunction are related to low sphincter pressure and disordered esophageal motility, with frequent non-propulsive contractions.
- Non-cardiac chest pain is caused by esophageal spasm related to abnormal motility.
- Urologic dysfunction is most likely related to detrusor muscle instability causing nocturia, urgency, and frequency.
- Gynecological complaints include pelvic pain and dyspareunia. IBS patients are more likely to undergo hysterectomy.
- Pulmonary symptoms result from increased airway responsiveness.

**Psychosocial issues**
- There is a higher frequency of depression, anxiety, panic, somatization, and personality disorders.
- Patients with IBS are more likely to view minor ailments as serious.

**Differential diagnosis**
- Neoplasia
- Inflammatory bowel disease (IBD)
- Infectious diarrhea, especially parasites
- Lactose intolerance
- Chronic diarrhea or constipation
- Gynecologic disorders
- Psychiatric disorders

**Preliminary modifications**
- Attempt to eliminate foods with high lactose, sorbitol, fructose or aspartame content.
- Consider a trial of alcohol and caffeine abstention.
- Eliminate or alter medications with gastrointestinal side effects, including over the counter medications such as magnesium containing antacids.
- Evaluate for major psychiatric disorders.
- If parasitic disease is a strong possibility, consider an empiric trial of metronidazole, given the low yield of ova and parasite collections.

**Recommended evaluation**
It is important for the physician to help the patient keep perspective during the evaluation. An overly extensive work up, with the attendant risks and costs, often causes more anxiety...
for IBS patients. The following tests should be considered if clinically indicated.

- Hemogram, electrolytes, liver function tests
- Fecal occult blood testing
- Stool for ova and parasites
- Bowel imaging – consider flexible sigmoidoscopy for age <50 and colonoscopy or barium enema plus sigmoidoscopy for age ≥50.
- If diarrhea is the predominant symptom, consider stool for fecal leukocytes, Sudan stain for fat, thyroid function tests, and/or biopsies on flexible sigmoidoscopy.
- If symptoms of upper gastrointestinal or biliary tract disease exist, consider endoscopy or abdominal ultrasound.

Treatment

Physician–patient relationship

- A trusting patient–physician relationship is essential. Too often patients have a sense that their doctors do not believe their symptoms.

Psychosocial aspects of management

- Make sure the patient understands that IBS is a real illness with active and quiescent periods, but that the long term prognosis is excellent.9
- Establish realistic expectations for symptom control rather than for a “cure”.
- Involve the patient in treatment decisions.
- Frequent, brief visits provide reassurance.

Therapeutic interventions

- Results of IBS therapy trials have been notoriously difficult to apply to clinical practice because of poor methodological design, non-uniform diagnostic criteria, ill defined outcome measures, and short follow up.10
- The remarkably high placebo effect typically noted in trials of IBS treatment, with up to half of control patients reporting benefits in many trials, lends support to the importance of the doctor–patient relationship in treatment of this illness.

Dietary modifications

As mentioned above, a change in diet may improve symptoms. Clinical data are conflicting, but since there are likely to be few ill effects, dietary change should be suggested in all patients. Dietary modifications also provide the patient with a greater sense of control and responsibility.

- Avoid the following: dairy products, caffeine, fatty foods, alcohol, and gas forming foods like legumes.
- Emphasize high fiber diet, possibly with supplementation.

Patients with IBS should not have findings suggestive of organic disease. Weight loss, fever, heme positive stools, rectal bleeding, pain or diarrhea that awakens the patient from sleep, anemia, onset of symptoms over age 50, family history of cancer or IBD should raise suspicion for other diagnoses.

9 Owens DM, Nelson DK, Talley NJ. The irritable bowel syndrome: long-term prognosis and the physician–patient interaction. Ann Intern Med 1995;122:107–12. In this prospective study, survival in patients with IBS did not differ from expected survival and the diagnosis was unlikely to be changed to an organic disease during an average follow up period of 29 years. A positive physician–patient interaction was associated with fewer return visits for IBS.

IBS, perhaps more than any other commonly seen illness, requires the physician to evaluate each patient as an individual with a unique physiology and psychology. The treatments agreed upon by the doctor and patient can be viewed as clinical trials with N = 1.

10 Jailwaala J, Imperiale TF, Kroenke K. Pharmacologic treatment of the irritable bowel syndrome: a systematic review of randomized, controlled trials. Ann Intern Med 2000;133:136–47. Of 238 trials of IBS treatment identified in a literature search, only 28 were considered to be of high quality. Of seven trials with bulk forming agents, three improved bowel symptoms. All seven trials of smooth muscle (anticholinergic) relaxants found benefits for patients with abdominal pain, but none of these agents are approved for use in the US. Dicyclomine was only supported by a single, poor quality trial.

Hyoscyamine is used less frequently because it has systemic effects. Donnatal is a preparation with hyoscyamine plus atropine, scopo-lamine, and phenobarbital.
Table 25.1  Agents for irritable bowel syndrome.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage form</th>
<th>Usual dosage</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>For pain, gas, bloating</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dicyclomine (Bentyl)</td>
<td>10, 20 mg</td>
<td>10 mg PO</td>
<td>Anticholinergics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>before meals</td>
<td>contraindicated in</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>glaucoma and urinary</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>obstruction</td>
</tr>
<tr>
<td>Hyoscyamine (Cystospaz)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– with atropine,</td>
<td></td>
<td></td>
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<tr>
<td>scopolamine,</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>phenobarbital (Donnatal)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Belladonna</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– with butabarbital</td>
<td>Tabs/elixir</td>
<td>1–2 tabs</td>
<td>Slows transit; ↑ water and salt</td>
</tr>
<tr>
<td>(Butibel)</td>
<td></td>
<td>or 5–10 cc PO</td>
<td>absorption; ↑ sphincter tone</td>
</tr>
<tr>
<td>– with opium</td>
<td>Suppository</td>
<td>1–2 suppositories</td>
<td></td>
</tr>
<tr>
<td>(B&amp;O Suppretes)</td>
<td></td>
<td>per rectum as needed</td>
<td></td>
</tr>
<tr>
<td>– tincture of belladonna</td>
<td>10% extract</td>
<td>1–2 drops</td>
<td></td>
</tr>
<tr>
<td>For diarrhea, fecal soiling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loperamide (Imodium)</td>
<td>2 mg</td>
<td>2 mg PO bid</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(in IBS)</td>
<td></td>
</tr>
<tr>
<td><strong>For constipation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psyllium (Metamucil)</td>
<td>596 mg per g</td>
<td>1 tsp in</td>
<td>Bulk producing laxative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>liquid PO</td>
<td></td>
</tr>
<tr>
<td>Methylcellulose (Citrucl)</td>
<td>2 g per 19</td>
<td>1 tsp in</td>
<td></td>
</tr>
<tr>
<td></td>
<td>g</td>
<td>liquid PO</td>
<td></td>
</tr>
<tr>
<td>Calcium polycarbophil</td>
<td>625 mg</td>
<td>2 tabs PO</td>
<td></td>
</tr>
<tr>
<td>(Fibercon)</td>
<td></td>
<td>qd-qid</td>
<td></td>
</tr>
<tr>
<td>Amitriptyline (Elavil)</td>
<td>10, 25, 50 mg</td>
<td>10–25 mg PO</td>
<td>Anticholinergic. Sedation, dry</td>
</tr>
<tr>
<td></td>
<td></td>
<td>qHS</td>
<td>mouth, orthostatic</td>
</tr>
<tr>
<td>Desipramine (Norpramin)</td>
<td>25, 50 mg</td>
<td>10–25 mg PO</td>
<td>hypotension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>qHS</td>
<td></td>
</tr>
</tbody>
</table>

**Medications** (see Table 25.1)
The goal is to alleviate the predominant symptom.

**Abdominal pain, gas, bloating**
- Anticholinergics inhibit gastrointestinal propulsive activity. While evidence for dicyclomine (Bentyl) is weak, there are trials supporting the use of other anticholinergics that are not available in the US.10 Dicyclomine is reportedly more selective for mucosal tissue than hyoscyamine.
- Belladonna, an anticholinergic containing atropine and scopolamine, has been used for centuries to treat intestinal symptoms (and poison one’s enemies), although it has never been studied rigorously. It is available in several preparations (see Table 25.1).
Antidepressants in low doses seem to act as analgesics rather than as antidepressants or anticholinergics. Tricyclics are the most frequently studied and are often recommended for chronic abdominal pain unresponsive to other therapies (amitriptyline or desipramine).

Diarrhea, urgency, or fecal soiling
- Loperamide decreases intestinal transit, increases intestinal water and salt absorption, and strengthens rectal sphincter tone.

Constipation
- Psyllium, methylcellulose, calcium polycarbophil, and other fiber supplements have not been conclusively proven to provide benefit, but still warrant a trial in most patients.
- Mild osmotic laxatives such as milk of magnesia, lactulose, and polyethylene glycol can be helpful, but stimulating laxatives (senna, bisacodyl) should probably be avoided.

Psychotherapy
- Cognitive behavioral therapy may achieve stress reduction through the development of coping strategies. Elements of behavioral therapy can be helpful for all patients with IBS.
- Intensive psychotherapy is probably most beneficial in patients with anxiety, depression, and pain unresponsive to medical treatment. In one trial, patients who received psychotherapy in addition to medical care had lessening of anxiety, depression, pain, and diarrhea but not constipation. The study was limited by problems with randomization.

Alternative therapies
- Hypnotherapy and biofeedback have been studied only in small trials. They may be helpful in selected patients and are probably not harmful.
- Herbal medicines may be helpful, but there are no standards for safety and preparation. In a trial of Chinese herbal medications, 50–78% of patients in the treatment groups reported improvement versus 30% in the placebo group.

Conclusions
- The medical prognosis of IBS is excellent but there is high psychosocial morbidity.
- The physician–patient relationship is the basis for successful management of the condition.
- The role of medication is to relieve symptoms, not to cure the condition.
- Excessive diagnostic testing and therapeutic trials can result in complications, increased patient anxiety, drug induced side effects, and added cost.
Diagnosis
The evaluation of suspected liver disease must distinguish between hepatocellular disease and cholestatic liver disease.

History
- History should include country of origin, travel, medications, herbs, alcohol and IV drug use, sexual contacts, occupation, exposure to toxins, blood transfusions, tattoos.
- Review of systems should include weight loss, change in color of stool or urine, abdominal pain, nausea, vomiting, diarrhea, pruritus, malaise, rash, and joint pain.

Physical exam
- Eyes: scleral icterus
- Neck: jugular venous distension
- Abdomen: liver size, nodularity, pulsations, bruit, friction rub, ascites, prominent veins on the abdomen, spleen size, right upper quadrant masses.
- Skin: jaundice, spider angiomas, palmar erythema, petechiae, ecchymoses, excoriation
- Neurologic: tremor, ataxia, lethargy, confusion, asterixis
- Other: cachexia, testicular atrophy, gynecomastia

Laboratory tests
- Complete blood count, BUN/creatinine, urinalysis
- Liver enzymes: aspartate transferase (AST, SGOT), alanine transferase (ALT, SGPT)
- Biliary enzymes: alkaline phosphatase, $\gamma$-glutamyl transpeptidase (GGT), 5'-nucleotidase
- Liver excretion functions: total bilirubin, direct (conjugated) bilirubin
- Liver synthetic functions: prothrombin time, albumin, clotting factors
- Serologies: hepatitis A, B, C

Patterns of liver enzymes
- Cholestatic liver disease
  - Increased alkaline phosphatase and/or elevated conjugated bilirubin levels
  - Normal transaminases and albumin
  - Elevated GGT or 5'-nucleotidase levels confirm that the alkaline phosphatase is from liver, not bone.

- Hepatocellular disease
  - Transaminases are $>3$–4 times normal with ALT > AST.
  - Transaminases $>1000$ units/l are suggestive of viral hepatitis, acute drug toxicity, or ischemic liver injury.
  - Elevations of both conjugated and unconjugated bilirubin.

Potentially hepatotoxic medications
- Isoniazid
- Statins
- Acetaminophen
- Thiazolidinediones
- Phenytoin
- Tetracycline
- Trimethoprim-sulfamethoxazole
- Methotrexate
- $\alpha$-Methyldopa

Potentially hepatotoxic herbs
- Comfrey, germander, chaparral leaf
- Valerian root, mistletoe
- Skullcap mixture
- Margosa oil, pennyroyal oil
- Gorlobo herbal teas, mate tea
- Chinese herbs (tu-san-chi, jinbu-buan)
Alcoholic hepatitis
- Transaminases are <300 units/l
- AST >2 times ALT
- Slight elevations of ALT are non-specific and often idiopathic. They can be seen following fractures, after eating, and in elderly people.
- Bilirubin: jaundice usually appears when the total bilirubin is above 2–3 mg/dl.
- Conjugated hyperbilirubinemia suggests cholestasis.
- Unconjugated hyperbilirubinemia suggests hepatocellular disease, hemolysis, or Gilbert’s syndrome.
- Alkaline phosphatase is often elevated with normal bilirubin in fatty liver (most common in diabetic and obese people). Elevations may also occur with space occupying lesions (granuloma or cancer).

Other blood tests to evaluate hepatocellular disease
- HBV DNA and HCV RNA by polymerase chain reaction (PCR)
- α-Fetoprotein (hepatocellular carcinoma)
- Ethanol, acetaminophen levels
- Transferrin saturation, ferritin (↑ in hemochromatosis)
- Anti-smooth muscle antibody (autoimmune hepatitis)
- Anti-liver-kidney microsomal antibody, anti-LKM (autoimmune hepatitis)
- Antimitochondrial antibody (primary biliary cirrhosis)
- Serum protein electrophoresis (autoimmune hepatitis or α₁ antitrypsin deficiency)
- Ceruloplasmin (↓ in Wilson’s disease)
- Antinuclear antibody (autoimmune hepatitis)
- Antineutrophil cytoplasmic antibody (P-ANCA) (primary sclerosing cholangitis)
- α₁ Antitrypsin (deficiency associated with cirrhosis)
- Ammonia (hepatic encephalopathy)

Asymptomatic patients with abnormal liver enzymes
- In patients without symptoms, repeating the abnormal test should be the first step.
- For persistent isolated transaminitis, initial evaluation includes probing for alcohol, medication and herb use, and testing for hepatitis B and C.
- If these are negative, ferritin, ceruloplasmin and serum protein electrophoresis can be done to identify hemochromatosis, Wilson’s disease, autoimmune hepatitis, and α₁ antitrypsin deficiency.
- Ultrasound can evaluate for steatosis (fatty liver).
- Mild elevations of alkaline phosphatase are common and usually benign. For persistently elevated alkaline phosphatase (of hepatic origin), ultrasound is the best test for evaluating the bile ducts (see below). If ultrasound is normal,

Injection drug use is one of the most common vehicles for spreading viral disease. Dr Benjamin Fordyce Barker, a Bellevue physician, introduced the first hypodermic syringe to the US in 1856.

Transferrin saturation =

\[
\frac{\text{Iron}}{\text{Total iron binding capacity}}
\]

4 Pratt DS, Kaplan MM. Evaluation of abnormal liver-enzyme results in asymptomatic patients. N Engl J Med 2000;342:1266–71. Several studies of asymptomatic patients with elevated transaminases were reviewed. Depending on the population studied, the most common causes were alcohol, viral hepatitis, fatty liver, or idiopathic.

5 Rubenstein LV, Ward NC, Greenfield S. In pursuit of the abnormal serum alkaline phosphatase: a clinical dilemma. J Gen Intern Med 1986;1:38–43. Of 54 patients who presented with unexplained elevations of alkaline phosphatase on health screening, the PPV of an abnormal level was only 5% among non-pregnant patients with no history of cancer or liver or bone disease.
antimitochondrial antibodies can evaluate for primary biliary cirrhosis.

- Isolated elevation of unconjugated bilirubin is seen in Gilbert’s syndrome. This inefficiency of bilirubin uptake is considered a normal genetic variant, not a disease.
- If liver enzymes remain persistently elevated, liver biopsy may be required.

Imaging the liver and biliary tree

- **Radiograph:** of the abdomen visualizes only pigmented (calcium bilirubinate) gallstones. Cholesterol gallstones (85% of the total) cannot be visualized. Hepatomegaly may be seen.
- **Ultrasound:** is the best single test to evaluate the biliary tree and gallbladder.\(^6\)\(^7\) It can detect gallstones, gallbladder wall thickening, duct dilatation, and duct anatomy. It is usually the first test obtained when gallstones or cholecystitis is suspected. It is less helpful in diagnosing common bile duct stones (choledocholithiasis).
- **HIDA cholescintigraphy scan:** directly evaluates the patency of the cystic duct and is extremely accurate at diagnosing acute cholecystitis.\(^6\) Non-visualization of the gallbladder is diagnostic for cystic duct obstruction consistent with acute cholecystitis.
- **Oral cholecystography:** is rarely performed now, since ultrasound is simpler and more accurate.\(^6\)
- **Liver-spleen scintigraphy scan:** isotope is not taken up in areas of the liver where the reticuloendothelial system has been replaced by a tumor, cyst, or abscess. These areas appear “cold”.
- **Computed tomography (CT):** of the abdomen is best used to evaluate the liver for solid masses (tumor, abscess) and diffuse disease (fatty liver, hemochromatosis, glycogen deposition). Intravenous contrast dye is necessary when imaging the liver. CT scanning is less accurate than ultrasound at detecting gallstones.\(^7\)
- **Endoscopic retrograde cholangiopancreatography (ERCP):** Although ERCP cholangiograms offer excellent anatomic visualization of the biliary tree, ERCP is used more as a therapeutic than a diagnostic procedure. It is employed primarily to extricate common bile duct stones and relieve acute biliary obstruction.
- **Magnetic resonance cholangiopancreatography (MRCP):** is particularly helpful in diagnosing common bile duct stones.\(^8\) Absence of such stones on MRCP could spare a patient the more invasive ERCP. Presence of these stones might lead a surgeon to perform an open cholecystectomy in centers where laparoscopic procedures are not available for common bile duct stones.
- **Helical CT cholangiography:** is a newer modality that may help identify common bile duct stones when MRCP is contraindicated or not available.\(^9\)
Percutaneous needle liver biopsy
- Indications
  - Persistently abnormal liver tests
  - Persistent unexplained hepatomegaly or cholestasis
  - Suspicion of infiltrative diseases (sarcoid, miliary TB)
  - Fever of unknown origin
  - Suspicion of malignancy (primary hepatoma or metastatic disease)
  - Staging of chronic hepatitis B or C
- Risks include bleeding, infection, and pneumothorax.
- Contraindications include coagulopathy, tense ascites, septic cholangitis, right sided pleural infection. Liver biopsy should not be performed if echinococcal cyst or vascular lesion is suspected.

Gallstones
Diagnosis
- Gallstones themselves generally do not cause symptoms. They are commonly diagnosed during imaging studies for other indications.
- Risk factors for gallstones include female sex, aging, obesity, rapid weight loss, malabsorption, pregnancy, cirrhosis, sedentary lifestyle, and diabetes.
- Biliary colic is perceived when there is inflammation or obstruction due to stone migration into the cystic or common bile duct. The sudden onset of episodes of severe, steady, right upper quadrant pain can be accompanied by nausea, vomiting, and mild bilirubin elevations.
- Fever and chills suggest complications of gallstones: acute cholecystitis, cholangitis, or pancreatitis.
- Diagnosis can be made with ultrasound, HIDA scan, or oral cholecystogram.

Treatment
- Treatment options are surgical, medical, and expectant management.
- The advantages of cholecystectomy are definitive treatment and prevention of future complications. Surgery is generally well tolerated and has a low mortality rate, although some patients report problems with diarrhea.
- Although there are few prospective, head to head trials of laparoscopic versus open cholecystectomy, the laparos-copic procedure appears to be at least as effective and is associated with a more rapid recovery.
- Medical treatment with bile acids has waned since the advent of laparoscopic cholecystectomy. It is now used mainly for patients who are unable or unwilling to undergo surgery.
  - Limitations include poor efficacy, long treatment course (up to two years), high gallstone recurrence rate.

—Ursodiol is the most commonly used agent. Addition of a statin\textsuperscript{13} or chenodiol may increase efficacy. Medical therapy is sometimes used in conjunction with lithotripsy.

- Asymptomatic patients may choose between expectant management and early cholecystectomy; the evidence does not clearly favor one course over the other.\textsuperscript{14}

- It is not clear if diabetic people with asymptomatic gallstones should be treated any differently.\textsuperscript{15}

**Primary sclerosing cholangitis**

- Primary sclerosing cholangitis is a slowly progressive, autoimmune disease of the biliary tree. Insidious sclerosis of the bile ducts leads to cholestasis, cirrhosis, and liver failure.

- There is a strong association with inflammatory bowel disease (particularly chronic ulcerative colitis) and fibrosclerotic syndromes. There is a higher risk of colon cancer and bile duct cancer.

- Typical symptoms are those of intermittent biliary obstruction and acute cholangitis. Diagnosis is made by cholangiography showing thickened, beaded ducts.

- D-penicillamine, cyclosporine, methotrexate, cholestyramine, and ursodiol may relieve symptoms, but only liver transplantation will prevent early death.

**Non-viral liver disease**

**Alcoholic liver disease**

- Alcoholic fatty liver (steatosis) is usually asymptomatic and can reverse with cessation of drinking.

- Acute alcoholic hepatitis presents like viral or toxic hepatitis and is often accompanied by alcohol intoxication or withdrawal.

- Alcoholic cirrhosis develops insidiously, usually after a decade of drinking (see section on cirrhosis below).

**Steatosis (fatty liver)**

- Fatty infiltration of the liver is commonly seen in patients with obesity and diabetes. It is typically seen on ultrasound during evaluation of asymptomatic transaminitis. The clinical course is usually benign.

- Non-alcoholic steatohepatitis is a more serious illness in which inflammation and fibrosis are seen in addition to fatty infiltration. This can progress to cirrhosis.

**Hemochromatosis**

- Hemochromatosis is the most common genetic disease in Caucasians, with prevalence as high as 1 in 250 in northern Europeans. There is some evidence to suggest that screening may be beneficial.\textsuperscript{16}

- Increased intestinal iron absorption and subsequent iron deposition in the liver and other organs leads to cirrhosis, diabetes, arthritis, cardiomyopathy, and hypogonadism.

\textsuperscript{13} Tomida S, Ahei M, Yamaguchi TA. Combination therapy with simvastatin and ursodeoxycholic acid is more effective for cholesterol gallstone dissolution than is ursodeoxycholic acid monotherapy. J Clin Gastroenterol 1998;26: 287–91.

\textsuperscript{14} Ransohoff DF, Gracie WA. Treatment of gallstones. Ann Intern Med 1993;119:606–19. The authors attempted to model life expectancies for expected management vs prophylactic surgery. They were not able to find significant differences.

\textsuperscript{15} Del Favero G, Caro A, Megiato T et al. Natural history of gallstones in non-insulin-dependent diabetes mellitus. A prospective 5-year follow-up. Digest Dis Sci 1994;39:1704–7. 47 asymptomatic and 23 symptomatic patients with gallstones and diabetes were followed for five years. 15% of the initially asymptomatic group reported symptoms. 17% had surgery (only one case was emergent). In the other group, 48% had symptoms and 22% had surgery (two cases were emergent).

Diagnosis is made by transferrin saturation >45% or ferritin >300 micrograms/l and liver biopsy. Treatment is with weekly phlebotomy. Occasionally iron chelation is used.

Autoimmune hepatitis
- Autoimmune hepatitis is seen in young and middle aged women.
- Diagnosis is suggested by serum protein electrophoresis (polyclonal increase), anti-smooth muscle antibodies and anti-LKM antibodies. The diagnosis is confirmed by liver biopsy.
- Treatment is with glucocorticoids and azathioprine.
- Autoimmune hepatitis can progress to fibrosis and cirrhosis. Transplantation is often required.

Primary biliary cirrhosis
- This disorder of chronic inflammation of bile ducts is often seen in conjunction with other autoimmune diseases including thyroiditis, sicca syndrome, and the CREST syndrome (calcinosis, Raynaud’s phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias).
- It is usually diagnosed during investigation of an isolated elevation of alkaline phosphatase in asymptomatic middle aged women. Early symptoms can include fatigue and pruritus. Later symptoms include bone tenderness and jaundice. Diagnosis is made by antimitochondrial antibody and liver biopsy.
- Ursodiol17 and cholestyramine may provide symptomatic relief, but there is no definitive treatment other than liver transplantation.

Wilson’s disease
- Impaired copper excretion results in copper deposition in the liver and other organs. It is characterized by neuropsychiatric disease, Kayser-Fleischer rings, cirrhosis, and occasionally fulminant hepatitis in teenagers and young adults.
- Diagnosis is made by ceruloplasmin <20 mg/dl, eye findings, and liver biopsy.
- Treatment consists of copper removal with lifelong penicillamine, even in asymptomatic patients.

α₁ Antitrypsin deficiency
- The deficiency or lack of the protease α₁ antitrypsin is associated with emphysema and cirrhosis.
- Symptomatic disease presents in childhood. Adults may have asymptomatic disease that progresses to cirrhosis independent of the pulmonary disease.
- Diagnosis is made by lack of an α spike on serum protein electrophoresis or by direct measurement of α₁ antitrypsin.
Cirrhosis

- Cirrhosis is a generic term for a disease characterized by hepatic fibrosis and nodules which may lead to portal hypertension and eventual liver failure.
- Viral etiologies include hepatitis B and C, cytomegalovirus, Epstein-Barr, and herpes simplex. Schistosomiasis causes cirrhosis in developing countries.
- Non-infectious etiologies include alcohol, hemochromatosis, primary biliary cirrhosis, primary sclerosing cholangitis, Wilson’s disease, autoimmune hepatitis, α1 antitrypsin deficiency, toxins, medications, and severe right sided heart failure (cardiac cirrhosis).
- The clinical course of cirrhosis depends less on the etiology than on the degree of liver damage.

Diagnosis

- Firm, nodular liver, ascites, splenomegaly, spider angiomas, muscle wasting, peripheral edema.
- Elevated or normal liver enzymes, hyperbilirubinemia, prolonged prothrombin time, hypoalbuminemia, hypocholesterolemia, thrombocytopenia, anemia, hyponatremia, and elevated ammonia.

Treatment

Aside from liver transplant, treatment for cirrhosis is essentially supportive.

Ascites

- Small studies have shown spironolactone to be beneficial in lowering plasma volume in conjunction with a low sodium diet (≤2 grams per day). Fluid restriction may also be necessary. Furosemide, thiazides, or ethacrynic acid can be added as second agents with careful attention to the tenuous fluid status of most patients with cirrhosis.
- Some patients will fail conservative treatment and require therapeutic paracentesis. The issue of albumin replacement is still under debate.
- Transjugular intrahepatic portosystemic shunting (TIPS) is another temporizing measure for patients with refractory ascites. It may be a better option in patients without significant renal or neurological consequences of cirrhosis.

Spontaneous bacterial peritonitis (SBP)

- SBP may present with fever, chills, abdominal pain, worsening encephalopathy, or jaundice.
- Analysis of ascitic fluid can help determine antibiotic coverage, but empiric treatment must cover Gram negative rods, the most common causative organisms.
- Declining renal function during an episodes of SBP is a poor prognostic sign. Treatment with intravenous albumin to maintain plasma volume may be helpful.

18 Williams JW, Simel DL. Does this patient have ascites? How to divne fluid in the abdomen. JAMA 1992;267: 2645–8. In an analysis of three studies, bulging flanks, flank dullness and shifting dullness each had a /p59 LR of 2 in the diagnosis of ascites (with ultrasound as the reference standard).
20 Rosse M, Ochs A, Galberg V et al. A comparison of paracentesis and transjugular intrahepatic portosystemic shunting in patients with ascites. N Engl J Med 2000;342:1701–7. 60 patients with cirrhosis and refractory or recurrent ascites were randomized to TIPS or large volume paracentesis. At 45 months, 15 had died and one had a liver transplant in the TIPS group v 23 and one in the paracentesis group. This study excluded patients with encephalopathy, creatinine >3mg/dl, or bilirubin >5mg/dl.
21 Sort P, Navasa M, Arroyo V et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis N Engl J Med 1999;341: 403–9. 126 patients with SBP were randomized to cefotaxime with or without albumin. SBP was eradicated in nearly all patients. Renal impairment developed in 10% of those given albumin v 33% in the controls. At three months, mortality was 22% and 41%, respectively.
SBP recurs in up to 70% of patients. Small trials have shown that ciprofloxacin, trimethoprim-sulfamethoxazole, and norfloxacin can reduce the recurrence of SBP, but none has been large enough to demonstrate mortality benefits.

**Esophageal varices**
- Variceal bleeding is treated acutely with endoscopic sclerotherapy, ligation, or administration of vasoconstrictors (vasopressin, somatostatin, octreotide).
- While many bleeds stop spontaneously, rebleeding is common.
- Trials comparing endoscopic and medical therapy have come to differing conclusions, probably because endoscopic techniques vary between practitioners and institutions.
- β blockers, nitrates, and prophylactic ligation or sclerotherapy all appear to reduce bleeding rates, but no studies have shown clear mortality benefits.

**Coagulopathy**
- Cirrhosis impairs the synthesis of clotting factors. Splenomegaly causes thrombocytopenia.
- Treatment with vitamin K may improve a prolonged prothrombin time, but may not be effective in advanced cirrhosis.
- Patients should avoid aspirin and NSAIDs.

**Hepatic encephalopathy**
- Hepatic encephalopathy is characterized by alterations in mental status, personality, and behavior. Asterixis may be seen. The pathogenesis is unclear, but elevated ammonia levels are a marker.
- Precipitants include GI bleed, infection, renal failure, increased protein intake, CNS depressant medications, diuretics, constipation, and worsening liver function.
- Treatment is largely supportive, with correction of precipitants if possible. Lactulose, neomycin, and low protein diet may help to decrease colonic ammonia production.
- Flumazenil, a benzodiazepine receptor antagonist, has shown promise in selected patients.

**Hepatorenal syndrome**
- Hepatorenal syndrome is an alteration of fluid hemodynamics that results in avid sodium retention and renal failure. It often occurs in the setting of SBP. There are no adequate treatments and mortality is high.

**Liver transplantation**
- Liver transplantation is the therapy of choice for fulminant acute hepatic failure and progressive endstage liver disease refractory to medical therapy.
- There are more than 16,000 patients on the waiting list. In 1999, 4697 livers were transplanted.

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29. United Network for Organ Sharing data. (www.unos.org)
- Indications include fulminant hepatitis, chronic hepatitis, primary hepatocellular carcinoma, primary biliary cirrhosis, primary sclerosing cholangitis, hepatic vein thrombosis, and alcoholic cirrhosis with abstention > 6 months.
- Contraindications include AIDS, active drug or alcohol abuse, bacterial or fungal infections outside the hepatobiliary system, metastatic cancer, advanced cardiopulmonary disease, and uncorrected coagulopathies that would interfere with surgery.
- The five-year survival now averages 75%.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage forms (mg)</th>
<th>Usual dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diuretics for ascites</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spironolactone (Aldactone)</td>
<td>25</td>
<td>25–400 mg PO qd</td>
</tr>
<tr>
<td>Furosemide (Lasix)</td>
<td>20/40</td>
<td>20–160 mg PO qd</td>
</tr>
<tr>
<td><strong>Variceal bleed prophylaxis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propranolol (Inderal)</td>
<td>10/40/80</td>
<td>10–80 mg PO bid</td>
</tr>
<tr>
<td>Isosorbide mononitrate (ISMO)</td>
<td>20</td>
<td>20 mg PO bid</td>
</tr>
<tr>
<td><strong>↑Prothrombin time</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin K₁ (Mephyton)</td>
<td>5</td>
<td>10 mg PO qd</td>
</tr>
<tr>
<td><strong>SBP prophylaxis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimethoprim/ sulfamethoxazole (Bactrim DS)</td>
<td>160/800</td>
<td>1 tab PO qd</td>
</tr>
<tr>
<td>Ciprofloxacin (Cipro)</td>
<td>100/250/500/750 mg</td>
<td>250–500 mg PO qd or 750 mg q week</td>
</tr>
<tr>
<td>Norfloxacin (Noroxin)</td>
<td>400 mg tabs</td>
<td>400 mg PO qd</td>
</tr>
<tr>
<td><strong>Hepatic encephalopathy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactulose syrup (Cephulac)</td>
<td>10 g/15 ml</td>
<td>30–60 cc PO bid-id</td>
</tr>
</tbody>
</table>
Low back pain is a frustrating problem because of difficulties in both diagnosis and treatment. Most back pain is essentially idiopathic, and there is little to offer the patient that shortens the course of what is usually a self limited, benign condition. Moreover, therapy for back pain is difficult to evaluate because trials of physical treatments (spine manipulation, back belts, etc.) cannot be blinded.

**Epidemiology**

**Prevalence**
- Back pain is a nearly universal part of human experience.
- In 1997, there were 15775000 ambulatory care visits for back symptoms in the US.\(^1\) The yearly incidence of low back pain is 15\(\text{--}20\)% in the US.
- Two percent of the US population is disabled because of low back pain at any given time. Half of these cases are chronic.
- There has been a steady rise in back pain disability in developed countries over the last 50 years; modern medical care may have contributed to this rise by medicalizing the problem.

**Causes of low back pain**
- Up to 85\% of cases are idiopathic.\(^2\) Musculoligamentous injuries and degeneration of the intervertebral discs and facet joints are presumably the cause. Imaging, however, rarely yields a precise diagnosis.

**Herniated nucleus pulposus (slipped disc)**
- A herniation of the central gelatinous material (nucleus pulposus) of an intervertebral disc through its fibrous outer covering (annulus fibrosus), with irritation of the nerve root causing sciatica.
- Herniated discs are seen on CT\(^3\) and MR\(^4\) in \(\sim 20\)% of people with no symptoms of low back pain.
- Ninety-eight percent of lumbar disc herniations occur at L4–L5 or L5–S1 (the two most inferior discs).\(^2\)
- Posterolateral herniation is the most common pattern.
- Sciatica is 79\(\text{--}95\)% sensitive for herniated discs.\(^2\) In the absence of sciatica, the likelihood of a slipped disc as the cause of low back pain is \(< 1\)%.

**Spinal stenosis**
- A narrowing of the spinal canal that may produce a bony constriction of the cauda equina and nerve roots. It is usually seen in elderly patients.
- *Neurogenic claudication* is a presenting symptom of spinal stenosis: leg pain on walking or standing, relieved by sitting.


2 Deyo RA, Rainville J, Kent DL. What can the history and physical tell us about low back pain? JAMA 1992; 268:760–5. An indispensable synthesis of the data.


4 Boden SD, Davis DO, Dina ST, Patronas NJ, Wiesel SW. Abnormal magnetic-resonance scans of the lumbar spine in asymptomatic subjects: a prospective investigation. J Bone Surg Am 1990;72:403–8. 67 volunteers who had never had low back pain. A herniated disc was seen in 20\% of people under 60 and 36\% of people over 60.

**Sciatica**: Pain radiating down the leg below the knee along the distribution of the sciatic nerve, usually related to pressure on the lumbosacral nerve roots. Sciatica is one type of radiculopathy.
**Cauda equina syndrome**
- Extremely rare, but a bona fide neurosurgical emergency.
- Caused by massive mid-line disc herniation.
- Signs and symptoms include global or progressive motor weakness in the lower limbs, urinary retention or incontinence, fecal incontinence, and “saddle anesthesia” (loss of sensation over the perineum).

**Other causes of low back pain**
- Spondylolisthesis
- Cancer: primary and metastatic from breast, lung, and prostate
- Infection
- Compression fracture
- Ankylosing spondylitis

**Psychosocial factors**
- Psychosocial factors are more important risk factors for chronicity than biomedical symptoms and signs.
- Greater education level and a favorable perception of one’s general health are associated with less back associated disability.\(^5\)
- Malingering and secondary gain must be considered. Low back pain is the most common cause of disability in persons under 45.

**Diagnosis**
The diagnostic challenge in low back pain is to distinguish between:
- simple backache (degeneration of discs and facet joints or musculoligamentous injury)
- radiculopathy caused by a herniated disc or spinal stenosis. Motor weakness (foot drop) is more serious than numbness
- serious pathology: cancer, infection, fracture
- psychosocial amplifiers, including secondary gain.

**History**\(^6\)

**Red flags**
- **For cancer or infection**
  - History of cancer
  - Unexplained weight loss
  - Fever
  - Immunosuppression
  - Urinary tract infection
  - Intravenous drug abuse
  - Prolonged use of corticosteroids
  - Back pain not improved by rest
  - Age > 50
- **For fracture**
  - History of trauma
  - Prolonged use of corticosteroids
  - Age > 70

---


**Facet joints**: Each lumbar vertebra has four facets. The two superior facets of L5 form a synovial joint with the two inferior facets of L4, and so on.

**Radiculopathy**: Dysfunction of a nerve root caused by compression. Pain, numbness, weakness, or reduced reflexes in the corresponding dermatome are signs of radiculopathy.

Physical exam
- **Inspection** of the lumbar area for scoliosis.
- **Palpation** for vertebral tenderness, muscle spasm.
- **Straight leg raising** is a physical exam maneuver for diagnosing herniated discs. With the patient supine, the physician slowly raises the leg with the knee extended until pain occurs. At 30–60°, tension is transmitted to a nerve root tethered by an extruded disc. A positive straight leg raising test reproduces the patient's *sciatica* (leg pain, not back pain) on the ipsilateral side at 30–60°.

Testing the dermatomes for neurological deficits
- L4: sensory loss in the medial aspect of the foot
- L5: weak ankle and great toe dorsiflexion, sensory loss in the dorsum of foot
- S1: diminished ankle reflexes, sensory loss in the lateral foot

Non-organic physical signs
The following suggest exacerbating psychosocial factors or malingering.
- Overreaction during the physical exam
- Inappropriate superficial or widespread tenderness
- Non-dermatomal motor and sensory defects
- Pain on simulated axial loading by pressing on the top of the patient’s head
- Pain on simulated spine rotation (the patient’s arms are held at the side while the hips are rotated, with the shoulders and hips rotating together).
- Straight leg raising that improves when the patient is seated.

Blood tests
- **Erythrocyte sedimentation rate** and **complete blood count** with differential are appropriate in patients over 50 with back pain for >6 weeks or at risk for infection or cancer.

Imaging
Routine imaging is not recommended in the first month of symptoms except in the presence of red flags. After one month of symptoms, an imaging test is appropriate when surgery is being considered or if a serious condition is suspected.

Plain radiography
- Radiographs are not indicated in simple backache.
- Acute back pain is usually due to conditions which cannot be diagnosed by plain radiographs.
- Herniated discs cannot be diagnosed by plain films.
- Plain films can detect compression fractures, spondylolisthesis, and ankylosing spondylitis – all rare causes of back pain.
- Indications for plain films:
  - red flags
  - failure of one month of conservative treatment.

Scoliosis: lateral curvature of spine. Scoliosis may be permanent as a result of muscle and/or bone deformity or acute as a result of unequal muscle contraction from acute back strain.

Lordosis: anteroposterior curvature of the spine, with the convexity looking anteriorly. The spine of a person who is “doing the limbo” is lordotic. The thoracic and lumbar spine are normally lordotic.

Kyphosis: anteroposterior curvature of the spine, with the convexity looking posteriorly. The cervical and sacral spine are normally kyphotic.

One patient’s perspective...
The acupuncturist had stuck twelve needles into him on fifteen occasions, a hundred and eighty needles in all, not one of which had done a thing. Zuckerman sat shirtless in one of the acupuncturist’s eight treatment cubicles, the needles hanging from him, and reading *The New York Times* – sat obediently for fifteen minutes, then paid his twenty-five dollars and rode back uptown, jangling with pain each time the cab took a pothole. The vitamin doctor gave him a series of five vitamin B-12 shots. The osteopath yanked his rib cage upward, pulled his arms outward, and cracked his neck sharply to either side. The physiotherapist gave him hot packs, ultrasound, and massage. One orthopedist gave him “trigger-point” injections and told him to throw out the Olivetti and buy the IBM; the next, having informed Zuckerman that he was an author too, though not of “best-sellers,” examined him lying down and standing up and bending over, and, after Zuckerman had dressed, ushered him out of his office, announcing to his receptionist that he had no more time that week to waste on hypochondriacs. *Philip Roth. The Anatomy Lesson. New York: Farrar, Straus and Giroux, 1983.*

A full set of lumbar spine radiographs involves 150 times the radiation dose of a chest radiograph. Anteroposterior and lateral views are sufficient. Oblique views (to look for spondylolysis) are not routinely recommended.

Computed tomography (CT) and magnetic resonance (MR)
- MR and non-contrast CT scanning can diagnose herniated discs and spinal stenosis.
- CT or MR should be reserved for patients who are failing conservative management and may be candidates for surgery.
- CT or MR is also recommended to evaluate tumor, infection, fracture, or other space occupying lesions of the spine.
- The discovery of disc abnormalities by MR in patients with low back pain may be coincidental.\(^8\)
- MR delivers no ionizing radiation and is thus considered the safer procedure of the two.

Treatment
- Conservative therapy is used in the vast majority of cases.
- Self administered heat and cold at home is a treatment option, although the benefit is unproven.

Medical therapy
- Acetaminophen reduces low back pain; comparisons with NSAIDs are inconsistent.
- NSAIDs are effective, especially if taken at regular intervals, not as needed. Different NSAIDs are equally effective. NSAIDs are less effective at reducing nerve root pain from herniated discs.
- Muscle relaxants effectively reduce low back pain associated with muscle spasm.\(^9\) Comparisons with NSAIDs are inconsistent. There is some evidence that additional benefit is gained by using muscle relaxants in addition to NSAIDs versus NSAIDs alone,\(^10\) although this is controversial. Drowsiness is an important side effect.
- Opioids are sometimes necessary in severe cases, but should not be prescribed for more than two weeks. Acetaminophen with codeine is an appropriate first agent.
- Although there is consensus that psychosocial factors such as depression can worsen back pain and contribute to chronicity, antidepressants have not been found to improve chronic low back pain.\(^11\)

Lumbar spine manipulation
- One important manipulation maneuver consists of a high velocity, small amplitude thrust applied to the fully rotated lumbar spine. This sometimes produces a cracking sound.
- Manipulation provides some positive short term relief of acute low back pain.\(^12\)
Epidural injections
- The efficacy of epidural steroid injections with or without local anesthetic has not been established; the benefits, if any, seem to be of short duration only.\(^{13}\) Injections are an option for short term relief of radicular pain when conservative therapy fails and as a means of avoiding surgery.

Acupuncture
- Acupuncture is not recommended for acute low back pain. None of the studies reviewed in a meta-analysis\(^ {14}\) demonstrated an advantage of needling in the appropriate Chinese meridians over incorrect needling.

Other treatments not currently recommended due to lack of evidence demonstrating efficacy
- Steroids, phenylbutazone, colchicine
- Ultrasound
- Cutaneous laser treatment
- Transcutaneous electrical nerve stimulation
- Spinal traction
- Biofeedback
- Trigger point injections
- Ligamentous injections
- Facet joint injections
- Back belts

Activity
Bed rest
- Bed rest has not been shown to shorten the course of acute low back pain compared to a return to normal activity.\(^ {15}\)
- Best rest for >2–4 days is associated with worse outcomes due to deconditioning.
- Bed rest is no longer recommended for acute low back pain – provided, of course, that the patient is able to get out of bed.

Exercises
- It is doubtful that specific back exercises produce clinically significant improvement in acute low back pain.\(^ {16}\)
- Exercises can reduce recurrences after the acute phase has subsided.
- Exercise programs and rehabilitation can improve pain and function in the setting of chronic low back pain.
- The McKenzie extension exercises are the most widely used, but there is no consensus about which exercise regimen is best.

Normal activity
- Advice to remain active and to return to normal activity as soon as possible has shown better results than bed rest or exercises.\(^ {17}\)

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\(^{16}\) Faas A. Exercises: which ones are worth trying, for which patients, and when? Spine 1996;21:2874–8. This review of 11 randomized trials concluded that…
- in acute back pain, exercise therapy is ineffective
- in subacute pain, exercises with a graded activity program may have benefit
- in chronic pain, intensive exercises may have benefit.

**Lifestyle changes for patients**
- Avoid lifting very heavy loads.
- Avoid twisting and bending when lifting. Keep loads close to the body. Keep the back as vertical as possible. Bend the knees and use the thighs. Never lift loads while bending from the waist with straight legs (the “car trunk injury”).
- Maintain symmetry when carrying heavy loads: two 30-pound suitcases are better than one 60-pound suitcase.
- Avoid becoming obese.
- Use a footstool or shoe insoles when standing for long periods.
- Use a proper mattress and pillow.
- Use a chair with lumbar and thigh support, and arm rests. The ideal seat to back angle for non-desk work is 120°.
- Use a lumbar corset if one’s job involves frequent heavy lifting.

**Back surgery**

**Indications**
- A lesion demonstrated by CT or MR with corresponding symptoms.
- Neurological deficit or persistent disabling sciatica
- Failure of one month of conservative therapy

**Surgery for herniated discs**
- Standard discectomy provides better short term outcomes than conservative therapy. Long term outcomes are similar.\(^\text{18,19}\)
- Only 2% of patients with back pain ultimately undergo surgery for herniated disc.\(^\text{20}\)
- Conventional disc surgery is more effective than chemonucleolysis of the disc with injection of chymopapain under local anesthesia.\(^\text{21}\)

**Surgery for spinal stenosis**
- Surgery should be reserved for elderly patients whose activities of daily life are severely compromised.
- Surgery should generally not be considered in the first three months of symptoms.

**Surgery for spondylolisthesis**
- In very rare cases, slippage may affect nerve root function.
- Severe spondylolisthesis (slippage > 50% or a severe increase in affected joint motion) can be treated with surgical decompression and spinal fusion.

**Prognosis**
In the great majority of cases, low back pain is a benign, self limited disease with an excellent prognosis.\(^\text{22}\) Seventy-five percent of cases will resolve in < 4 weeks and 90% in < 3 months. It has been suggested that the more seriously low back pain has been treated, the worse the problem has become. The era


\(^{21}\) Muralikttan KP, Hamilton A, Kernohan WG et al. A prospective randomized trial of chemonucleolysis and conventional disc surgery in single level lumbar disc herniation. Spine 1992; 17:381–7. At one year, 18% of the chymopapain chemonucleolysis group versus 31% of the surgery group were completely free of pain.

**Discectomy**: surgical removal of all or part of a herniated disc.

**Microdiscectomy** involves visually aided surgical techniques. The procedure can be done percutaneously.

**Spinal fusion** uses bone grafts or metal devices to produce a rigid connection between adjacent vertebrae.

**Laminectomy**: removal of the bony lamina to decompress the nerve root.

of prolonged bed rest and aggressive imaging is over. Reassurance, analgesics prescribed at regular intervals, and rapid return to normal activities are the cornerstones of therapy in acute low back pain.

Table 27.1 Agents for low back pain.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage form (mg)</th>
<th>Usual dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Analgesics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen (Tylenol)</td>
<td>325,500</td>
<td>1000 mg PO q6h</td>
</tr>
<tr>
<td>Acetaminophen/codeine</td>
<td>325/30</td>
<td>2 tabs PO q6h</td>
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<tr>
<td>(Tylenol 3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin (Ecotrin)</td>
<td>325</td>
<td>650 mg PO q4–6h</td>
</tr>
<tr>
<td>Ibuprofen (Motrin, Advil)</td>
<td>400,600</td>
<td>400–800 mg PO q6h</td>
</tr>
<tr>
<td><strong>Muscle relaxants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclobenzaprine (Flexeril)</td>
<td>10</td>
<td>10 mg PO qd-bid (21 days maximum)</td>
</tr>
<tr>
<td>Methacarbamol (Robaxin)</td>
<td>500</td>
<td>500 mg PO qid</td>
</tr>
<tr>
<td>Baclofen (Lioresal)</td>
<td>10</td>
<td>10 mg PO qid</td>
</tr>
</tbody>
</table>
Introduction

- Menopause marks the end of spontaneous menstruation. It occurs as a result of the natural loss of ovarian follicular function. It is a stage of life rather than a disease.
- The average age at menopause is 51 years, with most women experiencing several years of gradual menstrual irregularity, hormonal fluctuation and varying degrees of menopausal symptoms prior to the cessation of menses (perimenopause).\(^1\)
- There are many cultural aspects to menopause. Hot flashes are experienced by most Western women, but are relatively rare in East Asian cultures.
- Women who undergo surgical menopause (bilateral oophorectomy) often experience abrupt symptoms.
- The average woman may spend one third of her life in the postmenopausal period; hence the perimenopausal period provides an opportunity for education about preventive health care.
- Hormone replacement therapy (HRT) can alleviate perimenopausal symptoms and both treat and prevent osteoporosis. It may protect against coronary artery disease, but the data are conflicting.

Diagnosis and evaluation

- Menopause is usually obvious by history alone, generally by the absence of menses for one year. If the diagnosis is in question (for example, early age or hysterectomy without oophorectomy), an FSH level >25–30 mIU/ml is confirmatory.
- While pregnancy is unlikely in the perimenopause, a β-HCG should be checked if pregnancy is suspected.
- Other etiologies for hot flash-like symptoms, such as thyroid and infectious disease, should be assessed if appropriate.
- Symptoms of menopause include: hot flashes, flushing, sweating, urogenital atrophy, sleeplessness, early morning awakenings, stress incontinence, dyspareunia, changes in libido, emotional lability, perception of memory loss, or changes in cognitive function.
- Perimenopausal evaluation includes mammogram, breast exam, pelvic exam, and PAP test in addition to assessing risk for cardiovascular disease, osteoporosis, and breast cancer.

Short-term HRT

Short-term HRT is indicated for the treatment of menopausal symptoms. The decision to use HRT depends on the extent to which symptoms are disabling and the patient’s willingness to tolerate side effects. Other treatments should also be considered.

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Contraindications to HRT: The true risks of HRT are unknown because women with these conditions have traditionally been excluded from clinical trials.

Absolute contraindications

- Breast, ovarian, or endometrial cancer
- Active thromboembolism or thrombophlebitis
- Undiagnosed vaginal bleeding
- Pregnancy
- History of thromboembolism

Relative contraindications

- Gallbladder disease
- Liver disease
- Hypertriglyceridemia
- Severe fibroids
Hot flashes

- Hot flashes and flushing are believed to be related to the rate of estrogen withdrawal and resultant vasomotor instability.
- Episodes generally last from 30 seconds to five minutes and occur to some degree in most perimenopausal women. They can be disabling in 10–15% due to frequent episodes, particularly at night, leading to insomnia and fatigue.
- Hot flashes generally regress spontaneously; they may persist for up to six years.
- Precipitants to avoid include large meals, alcohol, caffeine, hot pepper, hot drinks, coffee, and tea. Wearing loose fitting clothes and keeping ice water nearby can be helpful.
- HRT given continuously or cyclically is extremely effective against hot flashes² (see below for dosing).
- Clonidine, a centrally acting α agonist, has been shown to decrease symptoms.³ It can be used orally or transdermally. Side effects include drowsiness, dry mouth, and dizziness.
- Megestrol acetate, a progestin, has shown some efficacy in women who have had breast cancer, as well as men with prostate cancer who have been treated with androgen deprivation therapy.⁴
- Alternative therapies are used by many women who do not wish to take HRT, but the few trials that have been undertaken have shown weak, if any, effects on menopausal symptoms.
- Isoflavones⁵,⁶ in soy products are estrogen-like compounds that bind to estrogen receptors. Consumption of whole soy foods (soy milk, tofu, soy nuts) has not been shown consistently to relieve symptoms, but is probably not harmful.
- Vitamin E and vitamin B complex are frequently used, but there are no studies evaluating them.
- Sage, black cohosh, fennel, ginseng and dong quai are herbs that have been used in various preparations but the few trials available do not support their effectiveness.

Urogenital atrophy

- The vulva, vagina, urethra, and trigone of the bladder all have large numbers of estrogen receptors. Menopause related symptoms can include vulvovaginal pruritus, bleeding, dyspareunia, incontinence, and increased frequency of cystitis.
- Intravaginal estrogen cream⁷ can provide relief, as can oral and transdermal preparations.
- Sterile, water soluble lubricants (Replens, K-Y Jelly) can also be helpful, especially for dyspareunia. Petroleum based products should not be used, as they can break down latex condoms and form a barrier against endogenous lubricants. Natural lubricants include vitamin E oil, olive oil, and sesame oil.
- Kegel exercises of the pelvic diaphragm and bladder training can help incontinence.

Mood, cognitive function, libido

- Although estrogen binding sites exist in various areas of the CNS, there is controversy as to whether declining hormone
levels contribute directly to the CNS symptoms of menopause.

- Symptoms seen during the perimenopausal period include depression, emotional lability, irritability, memory loss, inability to concentrate, and decreased libido. Frequent hot flashes and resultant insomnia, as well as underlying clinical depression, can contribute to many of these symptoms.

- Although observational studies have reported some improvement with HRT, randomized controlled trials with HRT or raloxifene have been inconclusive.

- The addition of testosterone may offer additional benefits in psychological and sexual function when estrogen therapy alone is not adequate. In a randomized trial of 75 women, transdermal testosterone at 300 micrograms, when added to estrogen 0.625 mg, improved sexual function as measured by a standardized questionnaire. This is theoretically important in oophorectomized women, who have much less testosterone than those with natural menopause.

**Long-term HRT**

The decision to use long term HRT depends on a woman’s risks for osteoporosis, heart disease, and breast cancer.

**Prevention and treatment of osteoporosis**

- Bone mineral density (BMD) declines most rapidly within two years of the menopause, when estrogen deficiency causes increased trabecular bone resorption.

- HRT halts the increased resorption of trabecular bone, creating an increase in BMD and continued protection from further loss as long as it is used. In the PEPI trial, BMD increased by 3.5–5.0% in the hip and 1.7% in the spine in all three HRT arms over three years, BMD decreased by 1.8% (spine) and 1.7% (hip) in controls.

- Although no large randomized trials assessing clinical outcomes have been completed to date, observational studies show an association between estrogen use and reduced risk for osteoporotic hip, wrist, and vertebral fracture.

- Bone densitometry is useful if the decision to use long term HRT is based solely on fracture risk. Screening recommendations for BMD were published in 1998 by the National Osteoporosis Foundation and are outlined in Chapter 31.

- For maximal prevention of fracture, HRT should probably be initiated within five years after the menopause and continued indefinitely, although it may be started at any age. A minimum therapy duration of seven years is required to confer some benefit to women >75 years, when the risk of fracture is greatest.

- Standard oral or transdermal HRT doses are used for prevention and treatment of osteoporosis. No trials of low dose HRT with fracture as an endpoint have been published to date.

-Raloxifene is a selective estrogen receptor modulator (SERM) that has estrogenic effects in bone and liver and antiestrogenic effects in the breast and uterus. It increases bone mineral density: results from the postmenopausal estrogen/progestin interventions (PEPI) trial. JAMA 1996; 276:1389–96.

- Prospective cohort of 9704 white women. Current estrogen users (mean duration 17 years) had a RR of hip, spine and wrist fractures of 0.29–0.50 compared to never-users. There was no difference between combined HRT and estrogen alone.

93 postmenopausal women with frequent urinary tract infections were randomized to intravaginal estriol or placebo and followed for eight months. Women in the treatment group experienced 0.5 vs. 5.9 episodes per patient year compared with placebo.


BMD and reduces vertebral, but not hip, fractures. Side effects include hot flashes and leg cramps. Progestins are not needed, as there is no endometrial hyperplasia.

- Alternatives to hormone based therapies are bisphosphonates. Alendronate and risedronate have been approved for both prevention and treatment of osteoporosis.
- In one study, bisphosphonates added to HRT increased BMD by 2–3% compared to placebo, but there is no evidence for a decreased fracture rate.

Primary prevention of coronary artery disease

- CAD is the leading cause of death in American women and the risk of CAD increases substantially after menopause, suggesting that estrogen may have some protective effect.
- Potential cardioprotective mechanisms of estrogens include beneficial changes in lipids, a decrease in fibrinogen levels, direct antiatherosclerotic effects in arteries, direct inotropic actions on the heart, and endothelium dependent vasodilatory and antiplatelet aggregating effects.
- The Women’s Health Initiative (WHI), the only large randomized trial evaluating HRT with respect to primary prevention of CAD, osteoporosis, breast cancer, and stroke, will conclude in 2007.
- The Nurses’ Health Study is the largest observational study. In multiple analyses, it has demonstrated a consistent reduction in CAD and cardiovascular mortality. On average, current users of HRT have a relative risk of 0.5 for CAD compared with never-users, regardless of the dose of estrogen or the addition of progesterone.
- The major criticism of this cohort study is that women who choose to use estrogen do not represent all women. On average, they are healthier, better educated, and in a higher socioeconomic class.
- Reduction in CAD risk may come at the expense of an increased risk for stroke (see below).
- Raloxifene has been shown in clinical trials to decrease total cholesterol and LDL, but no trials with CAD as an endpoint have been completed to date.

Secondary prevention of CAD: the HERS Study

- The Heart and Estrogen/Progestin Replacement Study is the only randomized, blinded, placebo controlled trial evaluating combination HRT (Prempro) in the secondary prevention of CAD.
- 2763 women with CAD were randomized to combination HRT or placebo and followed for nearly five years. There were 172 events (MI or cardiac death) in the treatment group compared to 176 in the placebo group.
- There were 34 thromboembolic events in the treatment group (13 in year 1) versus 12 in the placebo group.
- There was a pattern of early harm (year 1) and later benefit (years 3–5).
- Overall, there was no reduction in MI or CAD death at 4.1 years average follow up.

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14 Cummings SR, Black DM, Thompson DE et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 1998;280: 2077–82. A four-year randomized placebo controlled trial of 4432 women aged 54–81 found a significant 36% decrease in fracture risk at all sites for women with osteoporosis.
15 Harris ST, Watts NB, Genant HK et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA 1999;282:1344–52. 1600 women were randomized to placebo or risedronate 5 mg PO qd. 52 women in the control group had fractures v 33 in the treatment group after three years.
17 PEPI Trial Writing Group. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. JAMA 1995; 273:199–208. Women on HRT had a decrease in LDL of 16 mg/dl, an increase in HDL of 5 mg/dl, and an increase in triglycerides of 13 mg/dl.
19 Grodstein F, Manson JE, Graham A et al. A prospective, observational study Continued
Given the disappointing results of the HERS trial, HRT for the secondary prevention of CAD cannot be routinely recommended. However, due to the trend toward later benefit, it may be appropriate to continue therapy in women already receiving it.

Reduction of well known risk factors for CAD (hypertension, smoking, diabetes, obesity) should take priority.

**Risk of stroke**
- Initial data from the Nurses’ Health Study showed no significant association between stroke risk and use of HRT. However, in the most recent follow up a significant increase in stroke risk (RR = 1.54) was found for combined HRT (0.625 mg estrogen plus progestin). Estrogen use alone at all doses showed no significant association with stroke. No data were presented for 0.3 mg estrogen plus progestin use.

**Risk of breast cancer**
- Results from multiple observational studies of breast cancer risk with estrogen therapy are inconsistent. Studies vary considerably with respect to design, dosage, and duration.
- The best estimate of risk comes from the Nurses’ Health Study, which shows a relative risk of 1.4 among current HRT use (estrogen or estrogen plus progestin) for >= 5 years. This risk increases with increasing age (RR 1.7 for women 60–64). Use for less than five years was not associated with increased risk.
- Data from the MORE trial showed a 75% reduction in invasive breast cancer during three years of raloxifene therapy. In order to prevent one case of breast cancer, 126 women would need to be treated.

**Risk of venous thromboembolic disease**
- For the average healthy menopausal woman, the absolute risk of venous thromboembolism is small (about one per 10,000 women per year), but estrogens appear to increase this risk.
- In the PEPI trial of healthy women there was a non-significant increase with estrogen use.
- In the HERS trial of women with CAD, combined estrogen/progesterone gave a relative risk of 2.8, causing one case of DVT for every 339 women treated. 75% of cases were in women who had an underlying increased risk (recent lower extremity fracture, surgery, hospitalization, heart failure exacerbation, MI, stroke, or cancer).
- In the MORE trial, healthy raloxifene users had a relative risk of 3.1 for thromboembolic disease.

**Risk of endometrial cancer**
- Unopposed estrogen, at doses >=0.625 mg, carries a relative risk of endometrial cancer of close to 8.
- Addition of progesterone negates this risk. Women with a uterus are advised to take a progestin along with estrogen.
Raloxifene has not been shown to increase endometrial cancer.

**HRT regimens**
- It is important to review the goals of HRT (for example, treatment of menopausal symptoms versus prevention of osteoporosis) with the patient before initiating therapy.
- Efficacy of HRT should be assessed after 4–6 weeks; doses can be titrated upward until symptoms are relieved. The need for continued therapy can be evaluated every 4–6 months.
- HRT may be given orally, transdermally, or intravaginally, in either continuous or cyclical schedules.
- Progesterone is usually given with estrogen for women with a uterus to prevent endometrial hyperplasia.
- Women without a uterus do not require progesterone.
- Uterine bleeding that is excessive, prolonged, or in any way different from the expected bleeding of the prescribed regimens must be evaluated promptly with an endometrial biopsy and/or ultrasound.
- Premenstrual-like symptoms (breast tenderness, bloating, mood swings, headache) can occur when HRT is initiated. Many resolve spontaneously within a few months. Lowering the progesterone dose or switching from cyclical to continuous HRT can help.

**Standard dose continuous oral HRT**
- Conjugated equine estrogen (CEE) 0.625 mg PO daily with medroxyprogesterone acetate (MPA) 2.5 mg PO daily (Prempro combines these into one pill).
- Withdrawal bleeding occurs in a spotty, unpredictable manner, but usually abates after 6–8 months due to endometrial atrophy.

**Standard dose cyclical oral HRT**
- CEE 0.625 mg daily with 5 or 10 mg MPA on days 1–10 of each month.
- Withdrawal bleeding occurs monthly after day 10 of progestin and can continue for years.
- Cyclical HRT is available in a combination pill (Premphase); progesterone is present only in the pills for days 12–28.

**Low dose oral HRT**
- CEE 0.3 mg daily estrogen (with progesterone if needed)
- Low dose HRT may be sufficient to treat hot flashes in some women. Low dose HRT appears to preserve BMD, but there are currently no studies evaluating fracture risk.

**Transdermal HRT**
- Avoids first pass hepatic metabolism and has a theoretical advantage for women with a history of gallbladder disease, chronic liver disease, and hypertriglyceridemia.
- The patch is available with estrogen alone or in a combination of estrogen and progesterone.

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Common forms of estrogen (in equivalent doses)
- Conjugated equine estrogen (CEE, Premarin) 0.625 mg
- 17β-estradiol (Estrace) 2.0 mg
- Ethinyl estradiol (Estinyl) 0.02 mg
- Transdermal 17β estradiol (Climara, Estraderm) 0.05 mg

Common forms of progesterone
- Medroxyprogesterone acetate (MPA, Provera)
- Micronized progesterone
- Norethindrone

**Oral contraceptives (OCs)**
- Are often recommended for symptomatic perimenopausal women with regular or nearly regular menses (FSH < 20).
- Norethindrone acetate 0.5–1 mg plus ethinyl estradiol 20–35 micrograms is a common formulation.
- Provide an added benefit of pregnancy prevention, although the absolute risk of conception is low.
- Most women are switched to HRT when the FSH rises or at age 50, because the estrogen content of HRT is lower than in oral contraceptives.

Intravaginal HRT

- Systemic absorption is variable.
- Helpful for menopausal women in whom atrophic vaginitis is the predominant symptom and provides some relief for hot flashes.
- Typical use is cyclical (three weeks on, one week off).
- After atrophic vaginitis is relieved, some women are able to taper usage to once a week for maintenance.
- Concomitant progestins are not indicated for short term use but should be considered for long term use in women with a uterus.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage forms (mg)</th>
<th>Usual dose</th>
<th>Adverse effects, comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjugated estrogens (Premarin)</td>
<td>0.3/0.625/1.25/2.5</td>
<td>0.625 mg PO qd</td>
<td>Nausea; caution in liver disease</td>
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<tr>
<td>Medroxyprogesterone (Provera)</td>
<td>2.5/5/10</td>
<td>2.5 mg PO qd</td>
<td>Breast tenderness, bloating, breakthrough bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5–10 mg PO qd on first 10 days of each month</td>
<td></td>
</tr>
<tr>
<td>Conjugated estrogens plus medroxyprogesterone (Prempro)</td>
<td>0.625</td>
<td>1 tab PO qd</td>
<td>Nausea; caution in liver disease</td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td></td>
<td>Breast tenderness, bloating, breakthrough bleeding</td>
</tr>
<tr>
<td>Drug</td>
<td>Dosage forms (mg)</td>
<td>Usual dose</td>
<td>Adverse effects, comments</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>-------------------</td>
<td>------------</td>
<td>----------------------------------------------------------------</td>
</tr>
<tr>
<td>Estrogen vaginal cream (Premarin)</td>
<td>0.625 mg/g</td>
<td>0.5–2 g qd</td>
<td>3 weeks on, 1 week off</td>
</tr>
<tr>
<td>Estradiol transdermal system (Estraderm)</td>
<td>0.05–0.1 mg/24 h</td>
<td>1 patch twice a week</td>
<td>3 weeks on, 1 week off Must use oral progestins</td>
</tr>
<tr>
<td>Norethindrone acetate plus ethinyl estradiol (Femhrt 1/3)</td>
<td>1.0 5 microgram</td>
<td>1 tab PO qd</td>
<td></td>
</tr>
<tr>
<td>Calcium carbonate (Caltrate 600)</td>
<td>1500 mg (600 mg Ca)</td>
<td>1 tab PO bid</td>
<td>Constipating</td>
</tr>
<tr>
<td>Vitamin D (calcitriol) (Rocaltrrol)</td>
<td>0.25 microgram</td>
<td>0.25 microgram PO qd</td>
<td></td>
</tr>
<tr>
<td>Calcium carbonate plus vitamin D (Caltrate Plus)</td>
<td>1500 mg (600 mg Ca) 200 IU</td>
<td>1 tab PO bid</td>
<td></td>
</tr>
<tr>
<td>Alendronate (Fosamax)</td>
<td>10/70</td>
<td>10 mg PO qd or 70 mg PO q week</td>
<td>Alendronate and risendronate must be taken on an empty stomach; remain upright for 30 minutes to avoid reflux esophagitis</td>
</tr>
<tr>
<td>Risendronate (Actonel)</td>
<td>5/35</td>
<td>5 mg PO qd or 35 mg PO q week</td>
<td></td>
</tr>
<tr>
<td>Clonidine (Catapres)</td>
<td>0.1/0.2/0.3</td>
<td>0.1 mg PO qd-bid</td>
<td></td>
</tr>
<tr>
<td>Clonidine (transdermal) (Catapres-TTS)</td>
<td>0.1/0.2/0.3 per 24 h</td>
<td>1 patch q week</td>
<td></td>
</tr>
</tbody>
</table>
General approach

Diagnosis

Pattern recognition

- **Diffuse pain**: consider fibromyalgia, somatization, an acute flare of rheumatologic disease such as rheumatoid arthritis or systemic lupus erythematosus, or an acute viral syndrome.
- **Pain at many sites**: consider somatization, rheumatologic disease, and occupation related disease with repetitive microtrauma. Consider the diseases that may cause pain at one to several sites.
- **Pain at one to several sites**: focus on finding the source: joint, tendon, ligament, bursa, and/or nerve. Consider a rheumatologic process; monoarthritis or oligoarthritis may be due to crystalline arthropathy, spondyloarthropathy, or infectious arthritis.
- **Pain caused by intra-articular disease**: may be worsened by either passive or active motion. Isometric contraction without movement causes little pain or improves pain.
- **Tendinous pain**: is worse with active movement or isometric contraction, but is relatively unaffected by passive motion unless the tendon is overstretched.
- **Bursal pain**: is localized. There may be local swelling.
- **Pain of compressive neuropathy**: may be reproduced by placing pressure on the diseased portion of a nerve, causing symptoms in its distribution. There are usually associated neurologic symptoms and signs.

Additional history

- Injury
- Occupation or hobbies with repetitive motions
- Manifestations of autoimmune disease
- Psychiatric illness

Signs and symptoms requiring special attention

- Acutely inflamed joints (may require arthrocentesis to rule out infection).
- Low back pain in a patient with a history of malignancy.
- Pain associated with upper motor neurone disease, i.e. myelopathy.
- Pain so disabling that the patient is unable to manage at home.
- Referred pain (for example, angina radiating to the shoulder).
- Pain from acute trauma should be referred to an orthopedist if fracture or ligamentous derangement is considered.

Treatment

Non-Pharmacologic

- During the acute phase of injury, ice, compression, and elevation will reduce swelling. Ice also provides analgesia,

Proportion of Subjects from Different Countries with Persistent Pain (symptoms for six of the past 12 months)

<table>
<thead>
<tr>
<th>Location</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chile</td>
<td>33%</td>
</tr>
<tr>
<td>France</td>
<td>27%</td>
</tr>
<tr>
<td>Brazil</td>
<td>31%</td>
</tr>
<tr>
<td>India</td>
<td>19%</td>
</tr>
<tr>
<td>Washington</td>
<td>17%</td>
</tr>
<tr>
<td>China</td>
<td>13%</td>
</tr>
<tr>
<td>Nigeria</td>
<td>7%</td>
</tr>
<tr>
<td>All</td>
<td>22%</td>
</tr>
</tbody>
</table>


Top Five Industries with Disorders from Repetitive Microtrauma

<table>
<thead>
<tr>
<th>Industry</th>
<th>Rate per 1000 full time workers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meat packing</td>
<td>126</td>
</tr>
<tr>
<td>Knit underwear</td>
<td>101</td>
</tr>
<tr>
<td>Motor vehicle</td>
<td>96</td>
</tr>
<tr>
<td>Poultry processing</td>
<td>83</td>
</tr>
<tr>
<td>House slipper</td>
<td>73</td>
</tr>
</tbody>
</table>

but should be separated from the skin by a thin towel or plastic bag to prevent local tissue injury.

- A brief period of rest may be appropriate, but prolonged rest or immobilization should be avoided, as this may promote prolonged disability.
- In the subacute or chronic phase, application of heat may provide analgesia and decrease muscle viscosity to prevent reinjury during exercise therapy.

**Pharmacologic agents for pain relief**

**Acetaminophen**

- Acetaminophen should be first line therapy for non-inflammatory, non-traumatic disease.\(^1,2\)
- Studies have demonstrated equivalence between acetaminophen and NSAIDs for pain relief in non-inflammatory disorders such as osteoarthritis or tendinitis.

**Acetaminophen v NSAIDs in OA\(^1\)**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Change in pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen 4 g/d</td>
<td>-23%</td>
</tr>
<tr>
<td>Ibuprofen 1200 mg/d</td>
<td>-20%</td>
</tr>
<tr>
<td>Ibuprofen 2400 mg/d</td>
<td>-21%</td>
</tr>
</tbody>
</table>

**Non-steroidal anti-inflammatory agents (NSAIDs)**

- Indicated when a trial of maximum dose acetaminophen does not provide adequate relief.
- There is no proven benefit of one NSAID over another, but individual patients who have insufficient relief from one NSAID may experience relief after switching to another one.
- In patients with gastric ulcers or numerous erosions who cannot stop their NSAID therapy, proton pump inhibitors may help heal these lesions.\(^3\)
- Cyclo-oxygenase-2 (COX-2) inhibitors (celecoxib, rofecoxib) are NSAIDs that are designed to avoid GI toxicity.

**Incidence of Adverse GI Events in Patients Taking COX-2 Inhibitors v Non-Selective NSAID Therapy\(^4\)**

<table>
<thead>
<tr>
<th>COX-2 inhibitor</th>
<th>Non-selective NSAID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspepsia and abdominal pain</td>
<td>24.2%</td>
</tr>
<tr>
<td>Gastro-duodenitis</td>
<td>0.30%</td>
</tr>
<tr>
<td>Gastro-duodenal ulcers</td>
<td>0.48%</td>
</tr>
<tr>
<td>Non-ulcer bleeding</td>
<td>0.25%</td>
</tr>
<tr>
<td>GI bleed 2° to gastro-duodenal ulcer</td>
<td>0.25%</td>
</tr>
<tr>
<td>Gastric outlet obstruction 2° to gastro-duodenal ulcer</td>
<td>0.03%</td>
</tr>
</tbody>
</table>

**Tramadol**

- Tramadol has not been studied in large numbers of patients with osteoarthritis or soft tissue rheumatism, but it appears to provide relief in lieu of or in addition to other agents.

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4. Silverstein FE, Faich G, Goldstein JL et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal antiinflammatory drugs for osteoarthritis and rheumatoid arthritis: The CLASS Study: a randomized controlled trial. *JAMA* 2000;284:1247–55. Double-blind RCT of 8059 patients with OA or RA randomized to celecoxib 400 mg bid, ibuprofen 800 mg tid, or diclofenac 75 mg bid. Patients were treated for six months. NNT to prevent an NSAID induced ulcer was 455 patients.
Approximately 20% of patients will not tolerate it because of dizziness, nausea, headache, or fatigue.\(^5\)

Adverse reactions are reduced by 50% when the dose is started at 50 mg/d and increased by 50 mg/d increments every three days.\(^6\)

Narcotics
May be of benefit when used for brief periods.

### Pain Relief with Single Dose Codeine and/or Acetaminophen\(^7\)

<table>
<thead>
<tr>
<th>Treatment 1</th>
<th>Pain relief</th>
<th>Treatment 2</th>
<th>Pain Relief</th>
</tr>
</thead>
<tbody>
<tr>
<td>APAP/Codeine</td>
<td>22%</td>
<td>APAP</td>
<td>16%</td>
</tr>
<tr>
<td>APAP/Codeine</td>
<td>25%</td>
<td>Codeine</td>
<td>12%</td>
</tr>
<tr>
<td>APAP/Codeine</td>
<td>23%</td>
<td>Placebo</td>
<td>5%</td>
</tr>
<tr>
<td>Codeine</td>
<td>12%</td>
<td>APAP</td>
<td>17%</td>
</tr>
</tbody>
</table>

APAP: acetaminophen (N-acetyl-p-aminophenol) or paracetamol

Prolonged use of narcotics for non-malignant pain\(^8\)

- Problems with tolerance and with exacerbation of pain by subacute withdrawal may limit these agents’ effectiveness.
- There is inconsistent evidence for long term efficacy or improvement in functional status.

### Pain Relief for Osteoarthritis with Codeine/Paracetamol: Relative Benefit over Time\(^9\)

| Patients with pain better than at baseline |
|----------------|----------------|
| Codeine/paracetamol | Week 1 | Week 2 | Week 4 |
| Paracetamol        | 41%     | 40%    | 45%    |
|                    | 20%     | 31%    | 40%    |

Summary of narcotic use

- Narcotics should be reserved for the following subsets of patients:
  - patients with an intermittent or waxing and waning problem who will require brief periods of medication on occasion
  - patients who have chronic pain refractory to all other modalities. Narcotics may be of benefit in a subset of these patients.

- Narcotics should be avoided in patients with a history of substance abuse. If these patients require narcotics, consider referral to a pain specialist.

- In patients with chronic refractory pain, dosing should be around the clock with a long acting agent.

Corticosteroid injections

- May provide months of relief in OA and relief or cure in tendinopathies, bursopathies, and compressive neuropathies.

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\(^7\) De Craen AJM, Di Giulio GD, Lampe-Schoemaeckers AJEM, Kessels AGH, Kleijnen J. Analgesic efficacy and safety of paracetamol-codeine combination versus paracetamol alone: a systematic review. BMJ 1996;313:321–5. Most studies were of postoperative pain. There was no difference in side effect rates with a single dose.


\(^9\) Kjaersgaard-Anderson P, Nafei A, Skov O et al. Codeine plus paracetamol versus paracetamol in long-term treatment of chronic pain due to osteoarthritis of the hip. A randomised, double-blind, multi-centre study. Pain 1990;43:309–18. Patients were randomized to codeine 60 mg/paracetamol 1 g PO tid (83 patients) or paracetamol 1 g PO tid (75 patients). Adverse drug reactions caused patients to drop out of the trial in 48% of the codeine/paracetamol group and 14% of patients in the paracetamol group. Though there is not good evidence to support the practice, it is generally recommended that injection of corticosteroids into a single joint not be performed more than 3–4 times per year. Hochberg MC, Altman RD, Brandt KD et al. Guidelines for the medical management of osteoarthritis: osteoarthritis of the knee. Arthritis Rheum 1995;38:1541–6. Similarly, failure of symptoms of soft tissue disease to resolve after several injections suggests an alternative approach would be better.
There are unproven concerns about these injections causing tendon rupture or progression of OA.

Tricyclic antidepressants

- Useful for neuropathy
- May be useful for functional pain disorders, including somatization and fibromyalgia.

Arthritis

Osteoarthritis

Diagnostic criteria

- **Knees**:
  1. Knee pain and
  2. Osteophytes on radiograph or all of the following: crepitus, AM stiffness lasting <30 minutes, and clear, viscous synovial fluid with <2000 PMNs/cc.
- **Hips**: hip pain and at least two of the following:
  1. Erythrocyte sedimentation rate (ESR) <20 mm/h
  2. Osteophytes on radiograph
  3. Joint space narrowing on radiograph
- **Hands**: all of the following:
  1. Pain, aching, or stiffness
  2. Metacarpophalangeal (MCP) swelling in <2 joints
  3. Hard tissue enlargement of ≥2 of 10 hand joints
  4. Hard tissue enlargement of >2 distal interphalangeal (DIP) joints or deformity of ≥1 of the above joints

Treatment

- **Acetaminophen** is the first line oral agent, followed by NSAIDs.
- **Topical agents** (for example, methylsalicylate or capsaicin cream). Patients with OA of the hands or knees who do not desire or do not respond to oral agents may benefit.
- **Nutritional supplements**: a meta-analysis found probable benefit with chondroitin and glucosamine. A placebo-controlled three-year trial of glucosamine 1500 mg PO qd published after the meta-analysis found it to be effective in slowing the progression of joint space narrowing and symptoms.
- **Viscosupplementation with hyaluronic acid**: injections of these preparations (Hyalgan, Hylan G-F 20) provide pain relief and improved function for ~6 months. The cost of one course of therapy (five intra-articular injections for Hyalgan, three intra-articular injections for Hylan G-F 20) is approximately $600.

Hyaluronic Acid Injections in Treatment of OA of the Knees

<table>
<thead>
<tr>
<th>Week</th>
<th>Placebo</th>
<th>Hyaluronic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>62</td>
<td>66</td>
</tr>
<tr>
<td>5</td>
<td>41</td>
<td>28</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>32</td>
</tr>
<tr>
<td>4</td>
<td>48</td>
<td>33</td>
</tr>
<tr>
<td>6</td>
<td>54</td>
<td>39</td>
</tr>
</tbody>
</table>

(VAS: visual analogue scale)
- **Physical therapy** is of proven benefit in OA of the hip and knee.  

- **Weight loss:** the association between obesity and arthritis of the knee is strong. 

- **Aspiration of fluid followed by injection with corticosteroids** may be effective for short term pain relief that lasts several months. 

- Patients who require frequent injections may be candidates for arthroscopic lavage, joint debridement, or total joint arthroplasty.

### Rheumatoid arthritis

- The prevalence of RA is 0.7% in men, 1.6% in women. 

- **Diagnostic criteria:** the presence of at least four of the following criteria has a sensitivity of 94% and specificity of 89% (LR = 8.6). 

  1. Morning stiffness ≥1 hour 
  2. Rheumatoid nodules 
  3. Symmetric arthritis 
  4. Rheumatoid factor 
  5. Arthritis of ≥1 of wrist, MCP, or PIP 
  6. Arthritis of ≥3 of right or left wrist, elbow, knee, ankle, PIP joints, MCP joints, or metatarsalphalangeal (MTP) joints 
  7. Hand and wrist radiograph findings of erosions or unequivocal bony decalcification that is most marked in the area adjacent to the joint 

- All cases newly diagnosed or with progression of disease should be referred to a rheumatologist. 

### Gout

**Diagnosis**

- In gout, joint involvement is characteristically asymmetric. The first episode occurs in the first MTP joint in half of cases. Women often present after menopause with disease in other joints: ankles, tarsal-metatarsal joints, knees, wrists, and fingers. 

- Most patients have a second attack within two years after the first. 

- Negatively birefringent needle-shaped monosodium urate crystals in the synovial fluid are diagnostic of gout. These are observed in 95% of cases. 

**Treatment of an acute gout attack**

- Indomethacin (50 mg PO tid gradually tapering as symptoms subside) or colchicine in those who cannot tolerate NSAIDs (1.2 mg and then 0.6 mg every two hours until the onset of gastrointestinal symptoms). Adrenocorticotropic hormone (ACTH) or prednisone may also be used. 

- In a monarticular attack, intra-articular corticosteroids may be used if infectious arthritis has been ruled out. 

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17 Van Baar ME, Dekker J, Oostendorp RAB et al. The effectiveness of exercise therapy in patients with osteoarthritis of the hip or knee: a randomized clinical trial. *J Rheumatol* 1998;25:2432–9. Single-blind trial in which 210 patients were randomized to additional treatment with a physiotherapist for 12 weeks or to usual care by their physician. Benefits of therapy were similar for patients with OA of the hip and OA of the knee.

Outcomes 12 Weeks after Physical Therapy in OA of the Hip and Knee 

<table>
<thead>
<tr>
<th>Change in VAS score (0–100) for pain compared to baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise</td>
</tr>
<tr>
<td>Control</td>
</tr>
</tbody>
</table>

18 In a study of white women, the odds ratio of knee osteoarthritis was 9 for a 50% increase in weight. Hartz AJ, Fischer ME, Bril G et al. The association of obesity with joint pain and osteoarthritis in the HANES data. *J Chron Dis* 1986;39:311–19. 


20 Rheumatoid Factor: Likelihood Ratios at a Titer of 1:80

<table>
<thead>
<tr>
<th>Patient population</th>
<th>LR+</th>
<th>LR−</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary care clinic</td>
<td>37.6</td>
<td>0.22</td>
</tr>
</tbody>
</table>


Gout is the most common form of inflammatory arthritis in men over 40. Women usually do not have gout until after menopause.
Gout prophylaxis
- Low purine diet: reduced alcohol, meats, beans, lentils, asparagus, spinach, cauliflower, peas, mushrooms
- Colchicine 0.6 mg PO qd is indicated for prophylaxis after one severe attack or after disease recurrence.
- Allopurinol or probenecid should be prescribed if colchicine prophylaxis is inadequate or if serum uric acid cannot be reduced to <7 mg/dl by conservative means. These drugs should not be started until after the acute attack has resolved and should be used with another agent.

Infectious arthritis

Gonococcal arthritis
- The most common infectious arthritis in young adults.
- Initially, migratory arthralgias, tenosynovitis, and a vesiculopustular rash occur in approximately 65% of cases. Mono- or polyarthritis ensues.
- Cultures of blood, synovial fluid, pharynx, anus, vagina, and urethra are recommended.

Non-gonococcal arthritis
- Most non-gonococcal arthritis is caused by *Staphylococcus aureus*, followed by species of *Streptococcus*. Intravenous drug users are susceptible to *Pseudomonas*.
- Only 10–15% of non-gonococcal infections are polyarticular.
- The most common site is the knee, followed by the hip.
- All patients with acute monarticular arthritis of a large weightbearing joint or suspected gonococcal arthritis should undergo urgent arthrocentesis.
- Synovial fluid usually reveals 50,000–200,000 white blood cells, mostly polymorphonuclear leukocytes (PMNs).
- Gram stain is 75–95% sensitive in Gram positive infections.
- Patients with suspected infectious arthritis should be admitted for further management.

Fibromyalgia
- Prevalence in the US is 3–6 million patients.
- A history of widespread pain, and mild or greater pain in ≥11 out of 18 specified trigger points.
- The course of the disease is chronic and non-disabling, usually with some improvement over time.
- Treatment consists of patient education, light aerobics, stretching, and tricyclic antidepressants.
- Selective serotonin reuptake inhibitors may be of benefit.

Treatment of Fibromyalgia with Antidepressants

<table>
<thead>
<tr>
<th>Global Health (VAS 0–10)</th>
<th>Pain (VAS 0–10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 0</td>
</tr>
<tr>
<td>Placebo</td>
<td>5.9</td>
</tr>
<tr>
<td>Moclobemide</td>
<td>6.2</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>5.8</td>
</tr>
</tbody>
</table>

The diagnosis of acute gout requires the presence of PMNs with intracellular uric acid crystals.

Allopurinol or probenecid?
Allopurinol for patients with renal insufficiency, a history of kidney stones, markedly elevated uric acid, tophi, or hyperuricemia. Probenecid in underexcreters of uric acid (urinary urate <330 mg/24 h on a low purine diet). Probenecid predisposes to nephrolithiasis.


Arthrocentesis in Diagnosis of Inflammatory/Infectious Arthritis

<table>
<thead>
<tr>
<th>Test</th>
<th>Sens</th>
<th>Spec</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBCs &gt;2 × 10^9/mm³</td>
<td>84%</td>
<td>84%</td>
</tr>
<tr>
<td>PMNs &gt;75%</td>
<td>75%</td>
<td>92%</td>
</tr>
<tr>
<td>Glucose &lt;75 mg/dl</td>
<td>52%</td>
<td>56%</td>
</tr>
</tbody>
</table>


24 Goldenberg DL. Fibromyalgia syndrome: an emerging but controversial condition. JAMA 1997;278:792–7. High comorbidity with depression, chronic fatigue syndrome, somatization, and migraine, and poor interrater reliability on exam suggest that fibromyalgia may not be a discrete disease.


26 Hannone P, Malminniemi K, Ylikerttula U, Isomeri R, Ronponen P. A randomized, double-blind, placebo-controlled study of moclobemide and amitriptyline in the treatment of fibromyalgia in females without psychiatric disorder. Br J Rheumatol 1998;37:1279–83. Regimens: moclobemide 150 mg bid, amitriptyline 12.5 mg qHS, or placebo. Well designed trial. However, 25–33% of patients dropped out before the end of the trial; there was less dropout in the treatment groups than in the placebo group.
Common soft tissue disorders by anatomic site

**The shoulder**

**History**
- Most shoulder diseases do not present with pain in a specific location. Pain may present over the deltoid, in the area of the proximal triceps belly, or over the trapezius.
- **Biceps tendinitis**: there may be pain radiating down the anterior aspect of the upper arm.
- **Frozen shoulder**: restriction of range of motion in multiple directions; the pathologic correlate is adhesive capsulitis.
- **Glenohumeral instability**: there is a history of recurrent subluxation and/or dislocation or aching and occasional “dead arm” sensation.
- **Subacromial impingement syndrome**: impingement of the supraspinatus tendon (the most commonly affected tendon in rotator cuff tendinitis), the subacromial bursa, and/or the biceps tendon between the acromion and humerus.
  - History of occupational/athletic repetitive arm elevation.
  - There is a higher incidence in patients with diabetes.
  - Patients may report difficulty with activities of daily living that require arm elevation (for example, hair washing and grooming).

**Physical exam**
- **Subacromial impingement syndrome**: most tests are considered positive if the patient reports pain starting or worsening during the test. Selected tests are as follows:
  - Painful arc test: pain occurs between 60–120° of passive abduction and resolves above the level of that arc.
  - Yergason test: the elbow is flexed to 90° and the forearm pronated. The patient attempts supination against resistance. Pain over the bicipital groove indicates bicipital tendinitis.
  - Speed test: flexion is attempted against resistance starting with the elbow in extension and the wrist supinated. Pain over the bicipital groove indicates bicipital tendinitis.
  - Relief of pain by injection of lidocaine under the acromion is considered the gold standard.
- **Supraspinatus tear**: weakness on abduction
- **Frozen shoulder**: decreased range of abduction, internal rotation, and external rotation
- **Biceps tendinitis**: tenderness to palpation over the bicipital groove

**Treatment**
- Analgesia with acetaminophen or NSAIDs. Hot baths or showers relieve pain and improve ability to perform exercises.
- Patients with glenohumeral instability should avoid positions that provoke symptoms (for example, abduction with external rotation)

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27 Epidemiology of shoulder pain
Clinical diagnoses of shoulder pain among 335 patients in 11 Dutch primary care practices were 30% RC tendinitis, 13% chronic SA bursitis, 15% RC tear or mixed clinical picture, 22% frozen shoulder, 17% acute SA bursitis, and 13% other. Injury or chronic overuse was not reported in 49% percent of cases. *Van der Windt DAWM, Koes BW, de Jong BA, Bouter LM. Shoulder disorders in general practice. Ann Rheum Dis 1995;54:959–64.*

28 Operating Characteristics for Physical Exam Tests of Subacromial Impingement Syndrome

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speed</td>
<td>69</td>
<td>56</td>
</tr>
<tr>
<td>Yergason</td>
<td>37</td>
<td>86</td>
</tr>
<tr>
<td>Painful arc</td>
<td>33</td>
<td>81</td>
</tr>
</tbody>
</table>

*Calis M, Akgun K, Birtane M, Karacan I, Calis H, Tuzun F. Diagnostic values of clinical diagnostic tests in subacromial impingement syndrome. Ann Rheum Dis 2000;59:44–7.* Study of 120 patients with shoulder pain. Gold standard was injection of 10 cc 1% lidocaine into the subacromial space. All clinical tests were done by two physicians with an interrater reliability of 98%.
Patients with rotator cuff tendinitis, subacromial bursitis, and biceps tendinitis should avoid elevating the arm above 80°, flexion, or abduction.

All patients should be instructed in passive range of motion exercises below this plane while waiting to see a therapist to minimize the risk of consequent frozen shoulder.

Subacromial corticosteroid injections may be effective in patients with subacromial impingement syndrome and frozen shoulder, but heterogeneity of case definitions, outcome definitions, and results from different trials makes it difficult to form a conclusion.29,30

Referral to an orthopedist is indicated if there is unsatisfactory response to physical therapy or significant weakness suggestive of a tendon tear. In rotator cuff disease, symptoms >1 year, significant functional impairment, or rotator cuff tear ≥1 inch indicate poor non-operative outcome.31

The elbow

Classification

- **Lateral epicondylitis ("tennis elbow")** is the most common cause of elbow pain. Approximately 40–50% of recreational tennis players suffer from lateral epicondylitis at some point; however, 95% of patients with this diagnosis do not play any sports.32
- **Medial epicondylitis** accounts for ~10% of all cases of epicondylitis.
- **Cubital tunnel syndrome** (entrapment of the ulnar nerve) is the second most common compressive neuropathy of the upper extremity, after carpal tunnel syndrome.
- **Olecranon bursitis** is an area of fluctuant swelling over the extensor aspect of the elbow. It occurs with trauma or repetitive pressure to this area.

Diagnosis

- **Lateral epicondylitis**: tenderness is located up to 5 cm distal and anterior to the lateral epicondyle. Pain is aggravated by isometric wrist or finger extension while the elbow is in full extension and the wrist is placed in flexion.
- **Medial epicondylitis**: tenderness is anterior to the medial epicondyle and worsened by isometric pronation or wrist flexion.
- **Cubital tunnel syndrome**: there is medial elbow pain. Paresthesias often radiate to the fourth and fifth digits. Percussion of the ulnar nerve as it passes along the dorsal aspect of the medial epicondyle may reproduce symptoms. Nerve conduction studies help to clarify the diagnosis.
- **Olecranon bursitis**: Gram positive infection or crystalline arthropathies also cause this disorder; these must be ruled out by bursal fluid analysis.
- Consider radiographs to assess for post-traumatic arthritis or calcification.

---

29 In 100 patients with RC tendinitis, both NSAID and injectable corticosteroid performed better than placebo in various outcome measures. Corticosteroid was superior to NSAID in this study, but for many endpoints the difference was not statistically significant. Petri M, Dobrow R, Neiman R, Whiting-O’Keefe Q, Seaman WE. Randomized, double blind, placebo-controlled study of the treatment of the painful shoulder. Arthritis Rheum 1987;30:1040–5.


Treatment
- Patients should avoid activity that causes symptoms.
- Physical therapy may be of benefit. Splinting is often employed for symptomatic relief of epicondylitis.
- Olecranon bursitis:
  - Aspiration of fluid, protection of the bursa from pressure, compression with an elastic bandage, and NSAIDs.
  - Corticosteroid injection is appropriate if infection is absent.\(^{33}\)
- Epicondylitis: NSAIDs and corticosteroid injections are recommended for epicondylitis. These may provide rapid relief but do not alter the long term prognosis, which is generally good.

Treatment of Lateral Epicondylitis with NSAIDs v Placebo: Outcomes at 28 Days\(^{34}\)

<table>
<thead>
<tr>
<th>Change in VAS for Pain (0–100)</th>
<th>Side effects</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Placebo</td>
<td>16.0</td>
<td>9%</td>
</tr>
<tr>
<td>NSAID</td>
<td>29.9</td>
<td>30%</td>
</tr>
</tbody>
</table>

Treatment of Lateral Epicondylitis: 2 Weeks NSAIDs v Corticosteroid Injections v Placebo\(^{35}\)

<table>
<thead>
<tr>
<th>Elbow pain (Scale: 0–10)</th>
<th>Week 0</th>
<th>Week 4</th>
<th>Month 6</th>
<th>Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection</td>
<td>6.0</td>
<td>1.0</td>
<td>2.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Naproxen</td>
<td>4.0</td>
<td>4.0</td>
<td>1.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Placebo</td>
<td>5.0</td>
<td>3.5</td>
<td>1.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

- Surgery is usually effective in those who fail conservative therapy.

The hand and wrist

Ganglion cysts
- Ganglions, cystic masses associated with a joint or tendon sheath, are the most common tumorous lesions of the hands.\(^{36}\)
- A “ganglion cyst” presents as a firm mobile mass that may produce pain, numbness, or weakness; 60–70% are located on the dorsal wrist, 20% are on the radial anterior wrist.
- Physical exam by an experienced observer is usually sufficient to make the diagnosis. Plain films of the wrist or hand are recommended to assess for other causes of symptoms.
- Initial therapy consists of aspiration of cyst contents with a large bore needle, followed by instillation of a corticosteroid through a small bore needle (inserted prior to drainage).
- Treatment failure after up to three injections may warrant surgical treatment. Reports on benefit of therapy vary.

Carpal tunnel syndrome

Epidemiology\(^{37}\)
- Clinically defined CTS is present in 3.8% of people.
• The incidence of CTS is higher in rheumatoid arthritis, diabetes, and hypothyroidism and in patients who have jobs or hobbies that require repetitive wrist motion.

**Occupation and Carpal Tunnel Syndrome**

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Employees with CTS</th>
<th>Employees with bilateral CTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>2.4%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Employees engaging in repetitive tasks</td>
<td>11.8%</td>
<td>4.3%</td>
</tr>
</tbody>
</table>

**Diagnosis**

• CTS presents with numbness or tingling confined to the first, second, third, and radial half of the fourth digits; weakness on thumb abduction; or pain radiating distally and proximally from the wrist.

**Likelihood Ratios for History and Physical Findings in Carpal Tunnel Syndrome**

<table>
<thead>
<tr>
<th></th>
<th>LR+</th>
<th>LR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weak thumb abduction</td>
<td>1.7</td>
<td>0.6</td>
</tr>
<tr>
<td>Hypoalgesia</td>
<td>2.2</td>
<td>0.9*</td>
</tr>
<tr>
<td>Tinel sign</td>
<td>1.4*</td>
<td>0.8*</td>
</tr>
<tr>
<td>Phalen sign</td>
<td>1.3</td>
<td>0.7</td>
</tr>
<tr>
<td>Square wrist sign</td>
<td>2.7</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*P = non-significant

• Nerve conduction studies are reported to have sensitivity >90%, but only when motor, sensory, and mixed evaluations of the median nerve are combined. —Accuracy of these studies is determined by comparing to clinical parameters; they are not a gold standard. —These studies combined with electromyography are useful to assess for radiculopathy or ulnar nerve compression syndromes, which may be mistaken for or coexist with carpal tunnel syndrome.

**Treatment**

• Treatment consists of splinting the wrist in neutral position with a custom molded immobilization splint and local injections with a corticosteroid.

**Injection Therapy for Carpal Tunnel Syndrome**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>1 month</th>
<th>3 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroid plus lidocaine</td>
<td>77%</td>
<td>63%</td>
<td>50%</td>
</tr>
<tr>
<td>Lidocaine alone</td>
<td>20%</td>
<td>7%</td>
<td>7%</td>
</tr>
</tbody>
</table>

• Although patients frequently respond initially to these measures, many ultimately require surgical release.

---

38 Leclerc A, Franchi P, Cristofari MF et al. Carpal tunnel syndrome and work organization in repetitive work: a cross sectional study in France. *Occup Environ Med* 1998;55:180–7. The repetitive work group included employees from assembly lines, the food industry (packaging excluded), the clothing and shoe industry, and the packaging section of the food industry. Over 1500 employees were studied.


**Definitions for CTS by Hand Diagram**

• The patient must have symptoms in at least one of digits 1–3.
• The patient may have symptoms in digits 4–5, wrist pain, and radiation of pain proximal to the wrist.
• If the patient has palmar symptoms, they may not be confined to the ulnar aspect of the palm.
• No symptoms on the dorsum of the hand (but symptoms on the dorsum of the fingers are typical).

A copy of the hand diagram is presented in reference 39.

**Tests for carpal tunnel syndrome**

• **Phalen's test**: palmar flexion of the wrist to 90° flexion for 60 seconds reproduces paresthesias in the distribution of the median nerve.
• **Tinel's test**: repeated tapping of the central distal wrist crease over the median nerve causes paresthesias in the distribution of the median nerve.
• **Square wrist sign**: The AP diameter of the wrist divided by the mediolateral diameter is >0.70 (measure with calipers at the distal wrist crease).


41 Dammers JWHH, Veering MM, Vermeulen M. Injection with methylprednisolone proximal to the carpal tunnel: randomized double blind trial. *BMJ* 1999;319:884–6. The authors hypothesize that the benefit in this trial
**Trigger finger**

- Trigger finger is a snapping phenomenon as the fingers or thumb momentarily lock during active extension.
- Most are cured with a single corticosteroid injection into the flexor tendon sheath proximal to the MCP joint.
- Refer to a surgeon if multiple injections fail.

**The knee**

### Anterior knee pain

**Patellofemoral syndrome**

A poorly defined syndrome, without characteristic pathologic findings, caused by abnormalities of patellar and quadriceps mechanics. It probably represents a hodgepodge of disorders characterized by instability, misalignment, or neither.

- Of runners with knee pain, 50% have patellofemoral syndrome.
- The patient may describe increased crepitus, locking, or giving way.
- Symptoms are worse when climbing or descending stairs, squatting, and kneeling.
- Radiographs should be obtained to exclude patellofemoral osteoarthritis.
- In the acute phase, these patients should avoid climbing, jumping, squatting, running uphill, or kneeling.
- Long term outcome of non-operative treatment is excellent or good in 85% of patients.
- Physical therapy and/or a simple elastic sleeve may provide relief during overuse activities; however, there are no well designed randomized controlled trials.

**Patellar tendinitis**

- Tenderness is localized to an area over the tendon, usually its origin at the inferior aspect of the patella.
- Intense athletic training, training on hard surfaces, and repeated striking of the knee on the floor are risk factors.
- There is often a feeling of deepseated discomfort with prolonged sitting, as when driving or at the cinema.
- Pain is increased by isometric knee extension.
- Physical therapy is probably helpful; however, there are no well designed randomized controlled trials. Athletes probably need to refrain from training for a period.

**Chondromalacia patellae**

- A disorder with frank erosion of the articular surface of the patella. Increased crepitus is suggestive. The diagnosis can only be made by arthroscopy or arthrotomy.

**Bursitis**

- The most commonly affected sites in the knee are the prepatellar, suprapatellar, infrapatellar, and pes-anserine bursae.
- Presents with localized pain and swelling.
With prepatellar or infrapatellar bursitis, the bursa should be aspirated to exclude infection or crystal deposition.

Corticosteroid may be injected if there is no infection.

The patient should avoid kneeling.

Iliotibial band friction syndrome
- The most common cause of lateral knee pain in athletes.
- There may be a creaking sound over the lateral femoral condyle with flexion and extension of the knee.
- Joggers with this disorder should run on soft, level, uncantered surfaces. Physical therapy is usually effective.

Baker’s cyst
- Results from an abnormal communication between the synovial cavity of the knee and the semimembranosus-gastrocnemius bursa.
- Presents with popliteal pain and swelling. Ruptured cysts may mimic deep venous thrombosis.

Internal derangements
Anterior cruciate ligament (ACL) tear
- One of the most common knee injuries in sports (100,000 US skiers per year).
- Hemarthrosis at the time of injury is associated with a coexistent medial meniscal lesion >75% of the time.
- Classically, there is a history of the knee giving way, especially during pivoting.
- With chronic ACL insufficiency, the Lachmann test has an accuracy of 97% when performed by experienced clinicians.48

Medial meniscus tear
- The medial meniscus is torn more often than the lateral.
- The patient may have tenderness over the medial joint line.
- Meniscal injury may cause buckling or locking of the joint.
- This injury often occurs with the foot planted as the body rotates over the flexed knee.
- The McMurray test is 16–59% sensitive and 93–98% specific.49
- There are no trials comparing surgical to non-surgical management; thus, there is little evidence to argue for or against meniscal surgery. When performed, partial meniscectomy appears superior to total meniscectomy.50

The hip and buttock
Anterior pain
Osteoarthritis of the hip
- Presents with pain over the groin and anteromedial aspect of the thigh, occasionally radiating to the knee.
- Physical exam: pain and decreased range of motion are noted. The pain is exacerbated by passive extension and internal rotation.

References

The Lachmann test
The patient is supine, knee flexed to 15°, with the foot resting on the examining table. The examiner holds the distal femur fixed with one hand. The other hand holds the proximal tibia and pulls the tibia forward relative to the femur. In normals, a firm endpoint will be reached. With ACL insufficiency there will be greater forward translation of the tibia on the femur and the normal concavity of the patellar tendon will become convex.


The McMurray test
The patient is supine with the knee in full flexion. The examiner holds the knee so that the thumb is on the lateral aspect and the fingers are over the medial joint line. The other hand holds the foot in internal rotation. The foot is externally rotated as the knee is extended to 90°. A palpable thud along the medial joint line represents a positive test.

Athletic or traumatic injuries:51
- Iliopsoas tendinitis ("snapping hip"): there is an audible and palpable "clunk" as the hip moves from flexion to extension and the iliopsoas tendon snaps across the femoral head. The snapping sign may be mimicked by a labral tear.
- Acute groin pain: accounts for 3–5% of all sports injuries. The most common causes are strain of the muscle–tendon unit and post-traumatic occult hernia, associated with tenderness at the superficial inguinal ring.

**Lateral pain**
Trochanteric bursitis:52
- There is pain and tenderness over the greater trochanter, radiating down the lateral thigh in 25–40% of cases.
- Occasionally, pain radiates to the buttocks.
- Pain is aggravated by abduction or external rotation.
- Obvious swelling is unusual because of the deep location of this bursa.
- May be mimicked by L2–3 radiculopathy or occult stress fracture of the femur.
- Relief of pain with local lidocaine injection is diagnostic. Lidocaine may be coadministered with corticosteroid injection therapy.

Meralgia paresthetica
- Paresthesia over the lateral thigh; a benign condition occurring more commonly in obese patients.

**Posterior pain**
Ischiogluteal bursitis presents with tenderness over the ischium. Occurs with prolonged sitting.
- Sacroiliitis: pain is often worse at rest. There are usually abnormal findings on radiograph. The most common cause is osteoarthritis. HLA-B27 related diseases characteristically affect this joint.
- Lumbar radiculopathy: associated neurologic deficits
- Aortoiliac arterial disease: pain is worse with exertion. There is an abnormal peripheral vascular exam.

---


**Isometric Maneuvers in Diagnosis of Hip/Groin Muscle Strain**

<table>
<thead>
<tr>
<th>Pain with isometric:</th>
<th>implies Strain or tendinitis of:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trunk flexion</td>
<td>Rectus abdominis</td>
</tr>
<tr>
<td>Hip adduction</td>
<td>Adductor longus</td>
</tr>
<tr>
<td>Knee extension and hip flexion</td>
<td>Rectus femoris</td>
</tr>
<tr>
<td>Hip flexion and internal rotation</td>
<td>Iliopsoas</td>
</tr>
</tbody>
</table>
### Table 29.1  Agents for musculoskeletal pain.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage form (mg)</th>
<th>Usual dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Analgesics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen (Tylenol)</td>
<td>325, 500</td>
<td>1000 mg PO q6 prn</td>
</tr>
<tr>
<td>Acetaminophen/codeine (Tylenol 3)</td>
<td>325/30</td>
<td>2 tabs PO q6 prn</td>
</tr>
<tr>
<td>Tramadol (Ultram)</td>
<td>50</td>
<td>50–100 mg PO q6 prn</td>
</tr>
<tr>
<td><strong>NSAIDs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>325</td>
<td>650 mg PO q 4–6 prn</td>
</tr>
<tr>
<td>Ibuprofen (Motrin, Advil)</td>
<td>400, 600</td>
<td>400–800 mg PO q6 prn</td>
</tr>
<tr>
<td>Indomethacin (Indocin)</td>
<td>25, 50</td>
<td>25–75 mg PO tid prn</td>
</tr>
<tr>
<td>Naproxen (Naprosyn, Aleve)</td>
<td>250, 375, 500</td>
<td>250–500 mg PO bid</td>
</tr>
<tr>
<td><strong>Cyclo-oxygenase-2 inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celecoxib (Celebrex)</td>
<td>100, 200</td>
<td>100–200 mg PO bid prn</td>
</tr>
<tr>
<td>Rofecoxib (Vioxx)</td>
<td>12.5, 25</td>
<td>12.5–50 mg qd prn</td>
</tr>
<tr>
<td><strong>Gout Medications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allopurinol (Zyloprim)</td>
<td>100, 300</td>
<td>100–300 mg PO qd</td>
</tr>
<tr>
<td>Colchicine</td>
<td>0.6</td>
<td>0.6 mg PO qd</td>
</tr>
<tr>
<td>Probenecid (Benemid)</td>
<td>0.5 (scored)</td>
<td>0.25 mg PO bid × 7d the then 0.5 mg PO bid</td>
</tr>
</tbody>
</table>
30  Obesity
Corri Wolf

Epidemiology

Prevalence
• An estimated 97 million adults in the United States, 55% of the population, are overweight or obese (body mass index >25 kg/m²).1
• The NHANES study of 1988–94 indicated that 27% of females and 21% of males are obese (BMI >30).2
• The prevalence of obesity increased from 12% in 1991 to 18% in 1998. Increases were seen in both sexes and all socioeconomic classes, with the greatest increase seen in 18–29 year olds and in those who have achieved higher education.3
• Obesity rates are underestimated because overweight people tend to underestimate their weight and overestimate their height.4

Etiology
• Obesity is a chronic condition that develops as a result of an interaction between a person’s genetic makeup and their environment. How and why obesity occurs are not well understood; however, social, behavioral, cultural, psychological, metabolic, and genetic factors are involved.1
• Among possible causes of obesity, leptin, a hormone discovered in 1994, has received the most attention. Leptin appears to regulate adipose proliferation and modulate eating behavior.5 A 1999 study showed that subcutaneous therapy with recombinant leptin produced weight loss in both obese and lean subjects.6
• Heritability studies indicate that genetic factors may be responsible for up to 70% of the variability in weight.5
• Weight gain is dependent on a person’s energy intake being greater than energy expenditure. One pound is equal to 3500 calories. Therefore, a person consuming 500 calories more than he or she expends daily will gain one pound a week.
• A person’s body weight tends to range within 10% of a set value. Weight alterations in either direction cause changes in energy expenditure that favor return to the set point.7 This mechanism helps explain the terrible problem of recidivism following attempted weight loss.

Complications
• Relative risk8 >3: type 2 diabetes, gallbladder disease, hypertension, hyperlipidemia, sleep apnea
• Relative risk 2–3: coronary artery disease, knee osteoarthritis, gout
• Relative risk 1–2: breast, endometrial, colon cancer; low back pain
• The relationship between obesity and comorbidities is strongest among younger age groups.9 After age 74 there is

Guideline recommendations used in this chapter have been adapted from:
5 Yanozski JA, Yanozski SZ. Recent advances in basic obesity research. JAMA 1999;16:1504–6.
no longer an association between increased BMI and mortality.\textsuperscript{10}

- Hypertension is the most common obesity related disease. There is a strong association between hypertension and weight class in persons younger than 55 years old.\textsuperscript{11}
- Hyperinsulinemia, which is strongly associated with obesity, contributes to hypertension by activating the sympathetic nervous system and causing sodium retention.
- About 80% of type 2 diabetic people are obese.
- Hypercholesterolemia is very prevalent in obese persons, but its incidence does not increase with increasing weight class. The incidence of diabetes, osteoarthritis, and gallbladder disease increases as weight increases.
- Cardiovascular disease prevalence is significantly elevated for obesity class 1 in males and for all three obesity classes in females.

Diagnosis

Obesity is one of the easiest diagnoses in medicine; a glance at the patient is customarily all that is needed. The National Heart, Lung, and Blood Institute (NHLBI) classifies obesity according to BMI as follows.\textsuperscript{2}

<table>
<thead>
<tr>
<th>NHLBII Classification</th>
<th>BMI (kg/m\textsuperscript{2})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
</tr>
<tr>
<td>Normal</td>
<td>18.5–24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>25–29.9</td>
</tr>
<tr>
<td>Obesity class 1</td>
<td>30–34.9</td>
</tr>
<tr>
<td>Obesity class 2</td>
<td>35–39.9</td>
</tr>
<tr>
<td>Obesity class 3</td>
<td>&gt;40</td>
</tr>
</tbody>
</table>

Treatment

- Treatment methods for obesity have been shown to be ineffective over the long term. Over 90% of people who attempt to lose weight gain it all back.
- Even in clinical trials that demonstrate substantial weight loss, the lost weight tends to be regained once supervision concludes.
- On the positive side, sustained weight loss has been shown to improve blood pressure, lipids, and glucose levels.
- A reasonable goal is to lose 10% of body weight over a six month period.
- Patients with BMIs in the 27–35 range should be encouraged to lose 0.5–1 pound a week at a daily calorie deficit of 300–500.
- Patients with BMIs >35 should lose 1–2 pounds a week at a daily calorie deficit of 500–1000.

Diet

- A diet that is low in fat as well as total calories is needed to achieve weight loss.

\textsuperscript{11} Mikhail N, Golub MS, Tuck ML. Obesity and hypertension. Prog Cardiovasc Dis 1999;42:39–58.
• A healthy diet contains approximately 25% fat, 20% protein, and 55% carbohydrates.
• Total caloric intake is determined by calculating basal energy expenditure and activity, then subtracting 500 calories to result in a one pound weight loss per week.
• This usually means a diet of 1000–1200 kilocalories (kcal) per day for women and 1200–1500 kcal per day for men.
• Patients should be educated by a registered dietitian to eat a diet individualized to their needs.

Exercise
• Physical activity is a necessary component of every weight loss plan. Exercise contributes to weight loss and maintenance, may decrease abdominal fat, and increases cardiorespiratory fitness.
• Initial exercise goal: moderate activity for 30–45 minutes 3–5 days a week.
• Long term exercise goal: at least 30 minutes of moderate to intense exercise per day.1

Behavior therapy: advice for patients
• Eat three meals a day at approximately the same time each day sitting at a table.
• Focus on the meal. Eat slowly. Avoid distractions such as television or magazines.
• Cook small amounts; use small plates.
• Avoid second helpings. Clean plates directly into the garbage.

Drug treatment
• Pharmacologic therapy should be considered following failure of six months of diet, exercise, and behavior therapy in people with:
  —BMI >30 or
  —BMI 27–30 with coronary artery disease, diabetes, hypertension, hyperlipidemia, or sleep apnea.

Anorexiants (appetite suppressants)
• The majority of medications for obesity are sympathomimetics, pharmacologically related to the amphetamines. They are thought to suppress appetite by stimulating the satiety center in the hypothalamus.
• They are less than ideal agents due to their CNS stimulatory effects, side effects, abuse potential, and tolerance. They also raise blood pressure.
• Contraindications: use of other appetite suppressants or serotonergic drugs, severe hepatic or renal dysfunction, uncontrolled hypertension or coronary artery disease, heart failure, arrhythmias, and stroke.
• Interactions: possible serotonin syndrome with sumatriptan, SSRIs, venlafaxine, some opioids, lithium, or tryptophan. Patients should avoid excessive alcohol use. Anorexiants

Baseline energy expenditure (BEE)
Women:
18–30 years = (0.0621 × wt in kg + 2.0357) × 240 kcal/d
31–60 years = (0.0342 × wt in kg + 3.5377) × 240 kcal/d

Men:
18–30 years = (0.0630 × wt in kg + 2.8957) × 240 kcal/d
31–60 years = (0.0484 × wt in kg + 3.6534) × 240 kcal/d

Activity factor (AF):
Bed rest: 1.2
Ambulatory: 1.3
Normal activity: 1.5–1.75
Extremely active: 2.0

Injury factor (IF):
Minor surgery: 1.2
Skeletal trauma: 1.33
Elective surgery: 1.44
Major sepsis: 1.6–1.9
Trauma plus steroids: 1.88
Severe thermal burns: 2.1–2.5

Total energy expenditure = BEE × AF × IF

Commercial weight management programs:
Jenny Craig Inc.
445 Marine View Drive, Suite 300
Del Mar, CA 92014
619-259-7000

Nutri/System Inc.
380 Sentry Parkway
Blue Bell, PA 19422
215-940-3000

Weight Watchers International Inc.
Jericho Atrium
500 N. Broadway
Jericho, NY 11753-2196
516-939-0400
should not be prescribed with other drugs that increase blood pressure or pulse. Possible interaction with ketoconazole, erythromycin, and other drugs metabolized by CYP3A4.

- **Adverse reactions:** increased blood pressure and pulse, constipation, headaches, insomnia, dry mouth, dizziness, nervousness.
- The anorexic drugs fenfluramine (Pondimin) and dexfenfluramine (Redux) were withdrawn from the market in 1997 because of heart valve regurgitation and pulmonary hypertension seen in patients treated concurrently with phentermine (the “fen–phen” combination). Phentermine is still approved as monotherapy.
- In November 2000, the FDA requested that all drug companies discontinue marketing products containing the nasal decongestant/anorexic phenylpropanolamine because of an association with hemorrhagic stroke, especially in women. Phenylpropanolamine was marketed as an over the counter diet aid (Dexatrim, Acutrim).

**Phentermine (Ionamin)**
- Phentermine is the most commonly prescribed of the many anorectic agents.
- **Contraindications** include advanced arteriosclerosis, cardiovascular disease, hypertension, hyperthyroidism, glaucoma, agitation, and drug or alcohol abuse.
- **Side effects:** CNS stimulation, impotence, arrhythmias, hypertension, psychosis
- **Dosing:** 15–30 mg before breakfast.
- Phentermine has not been approved for long term use. It is an FDA Schedule IV controlled substance.

**Sibutramine (Meridia)**
- Approved by the FDA in 1997 for the long term treatment of obesity. Sibutramine has not been used in clinical studies for greater than one year.
- Sibutramine is unique in that it inhibits the reuptake of three neurotransmitters: norepinephrine, serotonin, and dopamine. In several trials it has been shown to cause weight loss when compared to placebo.
- In one trial, at 24 weeks the sibutramine group lost 3–5 kg more than the placebo group. At six months 69% of patients receiving 15 mg of the drug achieved a 5% reduction in their body weight. Improvement in lipid parameters (including an increase in HDL), reduction in waist–hip ratio, and improved glycemic control in type 2 diabetic patients have been seen as well.
- Adverse reactions seen in >10% of obese patients taking sibutramine include headache (30%), dry mouth (17%), constipation (12%), insomnia (11%), rhinitis (10.2%).
- Sibutramine is an FDA Schedule IV controlled substance.

**Other FDA-Approved Anorexiant Drugs**

<table>
<thead>
<tr>
<th>DEA schedule</th>
<th>Benzphetamine (Didrex)</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diethylpropion (Tenuate)</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>Mazindol (Mazanor, Sanorex)</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>Phendimetrazine (Bontril)</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>Phentermine (Ionamin)</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>Sibutramine (Meridia)</td>
<td>IV</td>
</tr>
</tbody>
</table>


Orlistat (Xenical)

- Approved by the FDA in 1999 for the long term treatment of obesity. Orlistat has not been used in clinical studies for greater than two years.
- Orlistat inhibits the absorption of dietary fat by binding to lipase in the lumen of the stomach and small intestine. Inactivated lipase is incapable of hydrolyzing triglycerides into absorbable monoglycerides and free fatty acids.
- Orlistat has been shown to promote significant weight loss (10.3 kg v 6.1 kg) in patients who consume a hypocaloric diet for one year. When patients switched to a weight maintenance diet and orlistat, they regained on average half as much weight as those taking placebo for one year.\(^{16}\)
- Similar results were seen in a study where patients lost weight on a hypocaloric diet and then took orlistat for weight maintenance. These patients regained significantly less weight than did the placebo group at one year (33% v 59%).\(^{17}\)
- Orlistat treated patients had significantly greater improvements in their lipid profiles, oral glucose tolerance test, waist circumference, and blood pressure.\(^{18}\)
- **Contraindications**: cholelithiasis, malabsorption syndrome. Caution with hyperoxaluria and calcium oxalate nephrolithiasis.
- Adverse reactions are common and intolerable to many patients: oily spotting, flatus with discharge, fecal urgency, increased defecation, and fecal incontinence.\(^{19}\) These side effects are worse following a high fat meal.
- **Interactions**: decreased absorption of the fat soluble vitamins A, D, E, and K. Supplement diet with a multivitamin with minerals two hours before or after medication.
- If a meal is missed or does not contain fat, the dose should be skipped. Patients should eat a diet that is <30% fat.
- Orlistat has been approved by the FDA for long term use. It is not a controlled substance.

**Surgery**

- Surgery has produced greater and more sustained weight loss than dietary or pharmacologic therapy.
- The most common surgical procedure is an upper gastric pouch that narrows the lumen and causes early satiety.
- Weight loss surgery is considered appropriate in patients with class 3 obesity or class 2 with comorbid conditions, when diet, exercise, and pharmacotherapy have failed, and who are at high risk for obesity related illness and death.
- The most common *gastric restriction* procedure is the vertical banded gastroplasty, which involves partial partitioning of the stomach at the proximal segment.
- The most common *gastric bypass* procedure is the Rouxen-Y esophagojejunostomy, in which a segment of jejunum is interposed between the esophagus and duodenum.\(^{1}\)


Table 30.1  Selected obesity drugs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage forms (mg)</th>
<th>Usual dose</th>
<th>FDA schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Norepinephrine releasers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzphetamine (Didrex)</td>
<td>25, 50</td>
<td>25–50 mg qd-tid</td>
<td>III</td>
</tr>
<tr>
<td>Diethylpropion (Tenuate Dospan)</td>
<td>75</td>
<td>75 mg qd 1 hour before meals</td>
<td>IV</td>
</tr>
<tr>
<td>Phendimetrazine (Bontril Slow Release)</td>
<td>105</td>
<td>105 mg 30–60 min before breakfast</td>
<td>III</td>
</tr>
<tr>
<td><strong>Norepinephrine reuptake inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mazindol (Mazanor, Sanorex)</td>
<td>1, 2</td>
<td></td>
<td>IV</td>
</tr>
<tr>
<td>Phentermine (Ionamin)</td>
<td>30</td>
<td>30 mg before breakfast</td>
<td>IV</td>
</tr>
<tr>
<td><strong>Mixed neurotransmitter reuptake inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sibutramine (Meridia)</td>
<td>5, 10, 15</td>
<td>10–15 mg qd</td>
<td>IV</td>
</tr>
<tr>
<td><strong>Lipase inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orlistat (Xenical)</td>
<td>120</td>
<td>120 mg tid 1 hour after meals</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** Medicaid does not pay for obesity drugs. The Schedule II drugs amphetamine (Dexedrine) and methamphetamine (Desoxyn) do not appear on this list because of their high abuse potential.

Table 30.2  Body mass index (kg/m²).

| Height (in) | 19  | 20  | 21  | 22  | 23  | 24  | 25  | 26  | 27  | 28  | 29  | 30  | 31  | 32  | 33  | 34  | 35  | 36  | 37  | 38  | 39  | 40  |
|-------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 4'10"       | 91  | 96  | 100 | 105 | 110 | 115 | 119 | 124 | 129 | 134 | 138 | 143 | 148 | 153 | 158 | 162 | 167 | 172 | 177 | 181 | 186 | 191 |
| 5'          | 97  | 102 | 107 | 112 | 118 | 123 | 128 | 133 | 138 | 143 | 148 | 153 | 158 | 163 | 168 | 174 | 179 | 184 | 189 | 194 | 199 | 204 |
| 5'1"        | 100 | 106 | 111 | 116 | 122 | 127 | 132 | 137 | 143 | 148 | 153 | 158 | 164 | 169 | 174 | 180 | 185 | 190 | 195 | 201 | 206 | 211 |
| 5'2"        | 104 | 109 | 115 | 120 | 126 | 131 | 136 | 142 | 147 | 153 | 158 | 164 | 169 | 175 | 180 | 186 | 191 | 196 | 202 | 207 | 213 | 218 |
| 5'3"        | 107 | 113 | 118 | 124 | 130 | 135 | 141 | 146 | 152 | 158 | 163 | 169 | 175 | 180 | 186 | 191 | 197 | 203 | 208 | 214 | 220 | 225 |
| 5'4"        | 110 | 116 | 122 | 128 | 134 | 140 | 145 | 151 | 157 | 163 | 169 | 174 | 180 | 186 | 192 | 197 | 204 | 209 | 215 | 221 | 227 | 232 |
| 5'5"        | 114 | 120 | 126 | 132 | 138 | 144 | 150 | 156 | 162 | 168 | 174 | 180 | 186 | 192 | 198 | 204 | 210 | 216 | 222 | 228 | 234 | 240 |
| 5'6"        | 118 | 124 | 130 | 136 | 142 | 148 | 155 | 161 | 167 | 173 | 179 | 185 | 191 | 197 | 203 | 209 | 216 | 222 | 229 | 235 | 241 | 247 |
| 5'7"        | 121 | 127 | 134 | 140 | 146 | 153 | 159 | 166 | 172 | 178 | 185 | 191 | 198 | 204 | 210 | 216 | 222 | 230 | 236 | 242 | 249 | 255 |
| 5'8"        | 125 | 131 | 138 | 144 | 151 | 158 | 164 | 171 | 177 | 184 | 190 | 197 | 203 | 210 | 216 | 223 | 230 | 236 | 243 | 249 | 256 | 262 |
| 5'9"        | 128 | 135 | 142 | 149 | 156 | 163 | 170 | 176 | 182 | 189 | 196 | 203 | 209 | 216 | 223 | 230 | 236 | 243 | 250 | 257 | 264 | 271 |
| 5'10"       | 132 | 139 | 146 | 153 | 160 | 167 | 174 | 181 | 188 | 195 | 202 | 209 | 216 | 223 | 230 | 236 | 243 | 250 | 257 | 264 | 271 | 278 |
| 5'11"       | 136 | 143 | 150 | 157 | 165 | 172 | 179 | 186 | 193 | 200 | 208 | 215 | 222 | 229 | 236 | 243 | 250 | 257 | 264 | 272 | 279 | 286 |
| 6'          | 140 | 147 | 154 | 162 | 169 | 177 | 184 | 191 | 199 | 206 | 213 | 221 | 228 | 235 | 242 | 250 | 258 | 265 | 272 | 279 | 287 | 294 |
| 6'1"        | 144 | 151 | 159 | 166 | 174 | 182 | 189 | 197 | 204 | 212 | 219 | 227 | 235 | 242 | 250 | 257 | 265 | 272 | 280 | 288 | 295 | 302 |
| 6'2"        | 148 | 155 | 163 | 171 | 179 | 186 | 194 | 202 | 210 | 218 | 225 | 233 | 241 | 249 | 256 | 264 | 272 | 280 | 287 | 295 | 303 | 311 |
| 6'3"        | 152 | 160 | 168 | 176 | 184 | 192 | 200 | 208 | 216 | 224 | 232 | 240 | 248 | 256 | 264 | 272 | 279 | 287 | 295 | 303 | 311 | 319 |
| 6'4"        | 156 | 164 | 172 | 180 | 189 | 197 | 205 | 213 | 221 | 230 | 238 | 246 | 254 | 263 | 271 | 279 | 287 | 295 | 304 | 312 | 320 | 328 |

Select row corresponding to patient’s height. Select patient’s weight in pounds within the row. Follow up vertically to the top row to identify the BMI.
31 Osteoporosis
Susan Urban

Epidemiology
Definitions of osteoporosis
- “A systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk.”
- Bone mineral density (BMD) > 2.5 standard deviations below the young adult mean reference group.
- Fragility fractures: these occur with minimal or no trauma, such as falling from a height of <12 inches or decelerating from a speed slower than a run. Fragility fractures affect mostly the spine, wrist, and hip.

Prevalence and incidence
- More than 28 million Americans have osteoporosis or low bone mass. Eighty percent of these are women.
- There are more than 1.5 million osteoporotic fractures in the United States per year. Most of these are fractures of the spine, wrist, and hip, but they can affect any bone.
- It is estimated that a 50 year old Caucasian man has a 13% lifetime risk of osteoporotic fracture.
- It is estimated that a 50 year old Caucasian woman has the following lifetime fracture risks.
  - Any osteoporotic fracture: 50%
  - Spine, wrist, or hip: 40%
  - Spine: 32%
  - Wrist: 15%
  - Hip: 16%

Pathophysiology
- Osteoporosis results from an imbalance of resorption and formation of bone. After peak bone mass is reached, bone continuously undergoes a process of remodeling in which it is broken down and rebuilt. There are approximately one million remodeling units in which osteoclasts are resorbing and osteoblasts are reforming bone. At any given time, about 10% of bone is undergoing remodeling.
- Type I osteoporosis is characterized primarily by increased bone resorption. It affects postmenopausal women between 51 and 71 years of age, affects primarily trabecular bone, and results mainly in spine and wrist fractures.
- Type II osteoporosis is characterized primarily by decreased bone formation. It affects women and men over the age of 71, affects cortical and trabecular bone, and results mainly in hip fractures.


4 Definitions adopted by the World Health Organization, 1994
Normal bone mineral density: within one standard deviation of the young adult mean.
Osteopenia or low bone mineral density: between 1 and 2.5 standard deviations below the young adult mean.
Osteoporosis: more than 2.5 standard deviations below the young adult mean.
Established or severe osteoporosis: more than 2.5 standard deviations and one or more fragility fractures.

5 The morbidity of osteoporosis results largely from fragility fractures: chronic pain, decreased mobility, and loss of independence. Mortality after a hip fracture can be as high as 25%.

Continued
Risk factors\textsuperscript{6–8}
- Increasing age
- Female sex
- Caucasian and Asian race
- Family history of osteoporotic fracture (especially the mother)
- Personal history of osteoporotic fracture
- Estrogen deficiency: postmenopausal, amenorrhea
- Diet deficient in calcium and vitamin D
- Lower level of peak bone mass
- Lack of weight bearing exercise
- Body weight <58 kg (<127 lb)
- Smoking
- Alcoholism

Secondary causes\textsuperscript{9}
- **Drugs**: steroids, anticonvulsants, long term heparin, excess thyroxine, methotrexate, lithium, cyclosporine, leuprolide.
- **Endocrinopathies**: hypogonadism (estrogen or testosterone deficiency), hyperthyroidism, hyperparathyroidism, Cushing’s syndrome, acromegaly, hyperprolactinemia, type I diabetes
- **Nutritional disorders**: alcoholism, calcium or vitamin D deficiency, protein malnutrition
- **Gastrointestinal**: malabsorption syndromes, subtotal gastrectomy, primary biliary cirrhosis, inflammatory bowel disease
- **Hematologic malignancies**: multiple myeloma, lymphoma, leukemia, systemic mastocytosis
- Rheumatoid arthritis
- Immobilization

Diagnosis

**History**
- Symptoms including back pain
- Menstrual history; menopausal status; sexual history
- Diseases or medications associated with osteoporosis
- History of fragility fracture
- Family history of fragility fractures or osteoporosis

**Physical exam**
- Height (loss of height)
- Weight
- Kyphosis
- Vertebral tenderness to palpation
- Stigmata of secondary causes

**Diagnostic tests**
- **Standard**: hemogram chemistry profile, thyroid stimulating hormone
- **As indicated**: 25-hydroxy vitamin D, parathyroid hormone, follicle stimulating hormone, luteinizing hormone, testosterone, dexamethasone suppression test, serum protein


\textsuperscript{6} The National Osteoporosis Foundation selected five risk factors for osteoporotic fracture:
1. low bone mineral density
2. history of prior fracture after age 40
3. history of fragility fracture in a first degree relative
4. weight \leq 58 kg (127 lb)
5. current cigarette smoking

Low bone mineral density is the most important predictor of fracture.

\textsuperscript{7} Risk factors for falls or prior history of falls are also important predictors of fracture. Ross PD. Osteoporosis: risk factors for osteoporotic fracture. Endocrinol Metabol Clin 1998;27:289–303.

\textsuperscript{8} Biochemical markers are important predictors of osteoporotic fracture. Markers of bone formation include serum osteocalcin and bone specific alkaline phosphatase. Markers of bone resorption include urinary type 1 collagen C-telopeptide.

\textsuperscript{9} Steroid induced osteoporosis occurs in 30–50\% of patients on long term steroids. Patients who will be on \geq 7.5 mg of prednisone daily for more than three months are vulnerable. Evaluation prior to starting steroids should include DEXA, blood tests, and 24-hour urine for calcium and creatinine. Patients should receive calcium 1500 mg qd and vitamin D 400–800 IU qd. Consider giving an antiresorptive agent, depending on the initial DEXA results. Patients should have a follow up 24-hour urine for calcium and creatinine in one month and a repeat DEXA in 6–12 months. American College of Rheumatology Task Force on Osteoporosis. Guidelines. Arthritis Rheum 1996;39:1791–810.

**DEXA results**:
- **T-score**: the number of standard deviations from the mean value for the normal young adult. T-score is used in the definition of osteoporosis.
- **Z-score**: the number of standard deviations from the mean value for the young adult of the same age and sex.
electrophoresis, sedimentation rate, 24-hour urine for calcium and creatinine, urine protein electrophoresis
• Thoracic and lumbar spine radiographs (for compression fractures)

**Dual-Energy X-ray absorptiometry (DEXA)**
• Currently the most common method for measuring bone mineral density.
• Measures bone density at the spine, hip, wrist, and total body.
• Low radiation: about one tenth the radiation of a chest radiograph.
• Reported as T-scores and Z-scores.

**Screening asymptomatic individuals by DEXA**
• Not yet routinely recommended but can be useful for screening high risk asymptomatic groups such as the following.
  —Women over the age of 65
  —Postmenopausal women less than 65 with risk factors for osteoporosis (not including being postmenopausal)
  —Premenopausal women with prolonged amenorrhea
  —Patients with chronic diseases or on long term medications associated with osteoporosis

**Diagnostic testing by DEXA**
• Postmenopausal women presenting with fractures.
• Premenopausal women and men presenting with fractures who have a clinical history compatible with osteoporosis.
• Patients with findings on radiograph or physical examination consistent with osteoporosis.

**Following bone mineral density over time**
• Follow up of treatment every 1–2 years
• Following the decrease in bone mineral density of selected patients not on treatment

**Treatment**

**General prevention**
• Smoking cessation
• Alcohol in moderation
• Exercise, both weight bearing (walking) and resistance
• Adequate calcium intake
• Adequate vitamin D from sunlight and/or diet

**Calcium supplementation**

**Daily Calcium Requirements – NIH Consensus Guideline**

<table>
<thead>
<tr>
<th>Women</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>11-24 years</td>
<td>1200–1500 mg</td>
</tr>
<tr>
<td>Premenopausal 25–50 years</td>
<td>1000 mg</td>
</tr>
</tbody>
</table>

deviations from the mean value for age matched patients. A low Z-score suggests that there may be a secondary cause of decreased bone mineral density.
DEXA spine measurement is not accurate if the patient has many osteophytes from degenerative disease, ligamentous calcification, or vertebral collapse. For this reason, measurement of hip BMD may be preferable in patients over the age of 65.
Quantitative computed tomography (QCT) is more accurate for spinal BMD than DEXA. However, the QCT is not a good test for following BMDs over time, since it results in more radiation and is more expensive than DEXA.
Quantitative ultrasound (QUS) has been approved to measure bone mineral density in the heel or shin bone. Advantages of ultrasound include lack of radiation exposure, lower expense, and portability. A prospective study showed that ultrasonography of the calcaneus predicted hip fracture as accurately as bone densitometry. Bauer DC, Gluer CC, Cauley JA et al. Broad-band ultrasound attenuation predicts fractures strongly and independently of densitometry in older women. Arch Intern Med 1997;157:629–34.

10 The first three indications for selective screening were adopted from the National Osteoporosis Foundation’s Physician’s Guide to Prevention and Treatment of Osteoporosis 1998.

11 Assessment of daily calcium intake The basic American diet excluding dairy provides about 250 mg of calcium per day. Each serving of dairy contains about 300 mg of calcium. The average American diet including dairy provides less than 600 mg of calcium. Adapted from Reference 10.

12 NIH Consensus Conference: Optimal Calcium Intake. JAMA 1994;272:1942–8. The National Osteoporosis Foundation recommends that women obtain at least 1200 mg of calcium per day including supplements. Adapted from Reference 10.
Postmenopausal on HRT 1000 mg
Postmenopausal not on HRT 1500 mg
All women >65 years 1500 mg

Men
25–65 years 1000 mg
All men over 65 1500 mg

• Patients who do not take in enough dietary calcium should take calcium supplements.

Calcium carbonate
• 40% elemental calcium by weight; therefore a 1500 mg pill contains 600 mg of elemental calcium
• Best absorbed if taken with food
• Decreased effectiveness in patients on H2 blockers and PPIs (achlorhydria)
• Side effects: constipation, flatulence
• Caution when history of renal stones

Calcium citrate
• 21% elemental calcium by weight
• Can be absorbed without food
• Effective in patients on H2 blockers and PPIs (achlorhydria)
• No major side effects

Recommendations for Adequate Intake of Vitamin D

People aged 19–50 200 IU
People aged 51–70 400 IU
People aged ≥71 600 IU

• Most multivitamin brands contain 400 IU of vitamin D.

Hormone replacement therapy (HRT)
Approved by the FDA for the prevention and management of osteoporosis.

Estrogen’s effect on bone
• Most evidence about the effect of HRT on fracture comes from observational studies. There are no controlled trials of HRT and hip or wrist fractures. Two clinical trials of primary and secondary prevention showed that estrogen decreased the risk of vertebral fractures.
• Slows bone loss in postmenopausal women.
• Decreases the fracture rate in postmenopausal women.
• Needs to be taken for at least 5–10 years to be effective on bone.
• Bone loss continues as soon as HRT is stopped.
• Most effective when started around menopause and continued lifelong, but can be useful when started later in life.
OSTEOPOROSIS

**Mechanism**
- Decreases bone resorption and bone turnover.
- Decreases osteoclast activity.
- Results in increased absorption of calcium from the GI tract.
- Results in decreased urinary excretion of calcium.

**Side effects**
- Breast tenderness
- Vaginal bleeding

**Risks**
- **Breast cancer**: some studies show a small increase in risk when HRT is used for more than five years.\(^{16}\)
- **Gallbladder disease**: two fold increased risk
- **Deep vein thrombosis and pulmonary emboli**: three fold increased risk. These events increase from about 10 per 100,000 patient years to 30 per 100,000 patient years in women over 50.
- **Endometrial cancer** if estrogen is used without a progestin in women with a uterus.

**Contraindications to estrogen**
- Known or suspected pregnancy
- Known or suspected breast cancer\(^{17}\)
- Known or suspected estrogen dependent neoplasia
- Undiagnosed genital bleeding
- Active thromboembolic disease
- Active liver disease
- History of thromboembolism
- Uneradicated endometriosis or enlarging fibroids
- Severe hypertriglyceridemia
- History of gallbladder disease

**Regimens**
- **Estrogen alone**: only in women without a uterus
- **Combined continuous**:
  - Premarin 0.625 mg PO qd plus
  - Provera 2.5 mg or 5.0 mg PO qd
- **Combined cyclic**:
  - Premarin 0.625 mg PO qd plus
  - Provera 5 mg or 10 mg PO qd for 12–14 days

**Alendronate**
- A second generation bisphosphonate, approved for the prevention and treatment of osteoporosis.

**Effect on bone**
- Increases bone mineral density.
- Decreases vertebral, wrist, and hip osteoporotic fractures in postmenopausal women by about 50%.\(^{18}\)

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\(^{16}\) Studies of the effect of HRT on breast cancer have had inconsistent results. One review found that HRT for five years was associated with two extra cases of breast cancer by age 70 in 1000 women. HRT for 10 years and 15 years was associated with six and 12 extra cases by age 70 in 1000 women respectively.


Results from the ongoing Women’s Health Initiative trial will help to clarify whether HRT increases the risk of breast cancer.

\(^{17}\) Clinical trials are under way to investigate the use of estrogen in breast cancer survivors.

Some practitioners consider the last four contraindications to estrogen to be relative, not absolute.

There are currently many formulations of estrogen and progesterone, in addition to Premarin and Provera, for use in the prevention and treatment of postmenopausal osteoporosis. These include pills and patches, both single hormone and combined.


Mechanism
- Decreases bone resorption and bone turnover.
- Binds to the hydroxyapatite crystals of bone and suppresses bone resorption by osteoclasts.
- Whatever is not bound is excreted unchanged in the kidneys.
- Lasts in the body for long periods – up to 14 years.

Side effects and risks
- Gastrointestinal symptoms, including heartburn, painful or difficult swallowing, chest pain, and esophageal or gastric ulceration. These GI effects were not more common in the treatment group in the clinical trials but have been observed in everyday clinical practice.

Contraindications
- Disorders of esophageal motility or structure
- Hypocalcemia
- Renal failure
- Patients who might become pregnant
- Patients unable to follow instructions or who are bedridden

Regimen and instructions
- Alendronate (Fosamax) 10mg PO qd for treatment and 5mg PO qd for prevention.
- Recently approved in a dosage of 70mg once weekly for treatment and 35mg once weekly for prevention.
- Take the pill first thing in the morning on an empty stomach with an 8-ounce glass of plain water. Do not take anything else (food, liquid, or pills) for the next half hour.
- Remain upright for the next half hour and until the next meal.

Raloxifene
- A second generation selective estrogen receptor modulator (SERM), approved for the prevention and treatment of osteoporosis. Raloxifene has estrogen-like effects on the bones and liver and antiestrogen-like effects on the breast and the uterus. Evidence for the effect of raloxifene on vertebral fracture comes from one clinical trial.19

Effect on bone
- Estrogen-like effect on the bone.
- Decreases bone resorption and turnover.
- Increases bone mineral density.
- Decreases the risk of vertebral fracture by about 30–50% in postmenopausal women with osteoporosis.19
- No evidence to date that it decreases the risk of hip fracture.

Side effects and risks20
- Hot flashes, leg cramps, peripheral edema.
- Increases the risk of deep venous thrombosis and pulmonary embolus about three fold.

Risedronate (Actonel), a third generation bisphosphonate, was approved by the FDA in April 2000 for the prevention and treatment of osteoporosis in a dosage of 5mg PO qd.

Risedronate was found to decrease the risk of vertebral and non-vertebral fractures in postmenopausal women who had at least one vertebral fracture at baseline by about 40%. Harris ST, Watts NB, Genant HK et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. JAMA 1999;282(14):1344–52.

In the MORE trial, raloxifene decreased the risk of invasive breast cancer by 76% during three years of Continued
• Does not cause breast pain or vaginal bleeding.
• No evidence that it causes endometrial cancer.

**Regimens**
• Raloxifene (Evista) 60 mg PO qd for prevention or for treatment without regard to food.
• Give with adequate calcium and vitamin D.

**Salmon calcitonin**
• A synthetic version of human calcitonin, approved for treatment of osteoporosis.

**Effect on bone**
• Increases or stabilizes bone mineral density.
• Decreases vertebral fractures.\(^{21}\)
• No evidence that it decreases the risk of hip fractures.
• Can decrease the pain of vertebral compression fractures.\(^{22}\)
• Inhibits bone resorption by acting directly on osteoclasts.

**Side effects**
• Rhinitis and other types of nasal mucosal injury
• Occasional nausea
• Occasional facial flushing

**Regimens**
• Nasal spray (Miacalcin) 1 spray (200 IU) qd
• Patients should alternate nostrils.
• The injectable form (Calcimar) is rarely used now.
• Give with adequate calcium and vitamin D.

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**treatment, with a 90% decrease in estrogen receptor positive tumors and no effect on estrogen receptor negative tumors. It decreased the risk of all breast cancer (both invasive and non-invasive) by 65%. Salmon calcitonin is 40–50 times more potent than human calcitonin. Human calcitonin is not approved for the treatment of osteoporosis.**


## Table 31.1 Agents for osteoporosis.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Approval</th>
<th>Comments/side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium carbonate* (Caltrate Plus D)</td>
<td>1500 mg (600 mg Ca) plus vitamin D 200 IU</td>
<td>Prevention</td>
<td>All treatments for osteoporosis require adequate calcium intake</td>
</tr>
<tr>
<td>Conjugated estrogens (Premarin)**</td>
<td>0.625 mg PO qd</td>
<td>Treatment</td>
<td>Breast pain</td>
</tr>
<tr>
<td>Medroxyprogesterone (Provera)</td>
<td>2.5 or 10 mg PO qd (see text for regimens)</td>
<td>Prevention</td>
<td>Vaginal bleeding Deep venous thrombosis (DVT) Pulmonary embolus (PE)</td>
</tr>
<tr>
<td>Alendronate (Fosamax)</td>
<td>10 mg PO qd or ... 70 mg PO q week</td>
<td>Treatment</td>
<td>GI side effects</td>
</tr>
<tr>
<td></td>
<td>5 mg PO qd or ... 35 mg PO q week</td>
<td>Prevention</td>
<td>See text for special instructions</td>
</tr>
<tr>
<td>Risedronate (Actonel)</td>
<td>5 mg PO qd</td>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>Raloxifene (Evista)</td>
<td>60 mg PO qd</td>
<td>Treatment</td>
<td>Hot flashes Periferal edema Leg cramps DVT/PE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prevention</td>
<td></td>
</tr>
<tr>
<td>Calcitonin (Miacalcin)</td>
<td>1 spray qd (alternate nostrils)</td>
<td>Treatment</td>
<td>Rhinitis Nausea, facial flushing</td>
</tr>
</tbody>
</table>

*Other forms of calcium are available. See text.

**Many other formulations of estrogens and progestins are available. See Chapter 28.
### 32 Palpitations
Damara Gutnick

#### Epidemiology

**Prevalence**
- In a 1990 study, palpitations were the tenth most common symptom reported in primary care.\(^1\)
- In an ambulatory elderly population, the prevalence of palpitations was 8.3%.\(^2\)
- Psychiatric illness accounts for the etiology of palpitations in nearly one third of all patients.\(^3\)–\(^5\)
- Outpatients with palpitations are more likely to have a psychiatric etiology than emergency room presenters (45% v 27%).
- Women are more likely than men to have panic disorder as the etiology of their palpitations.

#### Etiology
- Most healthy individuals are unaware of their resting heartbeat. Increased stroke volume, increased contractility, or changes in heart rate or rhythm may cause a patient suddenly to become aware of his or her heartbeat. This sudden perception can be disconcerting and incite fears of serious heart disease.

#### Diagnosis
- Palpitations may be the presenting symptom in a wide variety of medical and psychiatric disorders.\(^1\) In a prospective cohort study of 190 consecutive patients presenting with palpitations to the University of Pittsburgh Medical Center, a probable etiology was determined in 84% (159 patients):\(^3\)
  - 43% cardiac
  - 31% psychiatric: anxiety, panic attack, panic disorder
  - 10% other: medications, thyrotoxicosis, caffeine, cocaine, amphetamine, anemia
  - 16% unknown.
- The object is to identify patients at high risk for life threatening arrhythmias while minimizing testing in the vast majority of patients who have a good prognosis.
- In the Pittsburgh study,\(^3\) of the 159 patients who were assigned an etiology, 40% were diagnosed by only history and physical, ECG, and blood tests (TFTs, hematocrit, theophylline level).

#### History

**Description of the palpitations**\(^6\)
- Ask the patient to tap out the rate and rhythm of the palpitations. Is it regular or irregular? Fast or slow?
- Duration greater than five minutes suggests a cardiac cause.
- Complaints of a “flip-flopping” in the chest or the heart “stopping, then starting again” suggest premature beats.
The compensatory pause following a ventricular premature beat allows for prolonged filling time and the expulsion of an abnormally large volume of blood with the next stroke.

- "Pounding in the neck" suggests supraventricular re-entrant tachycardia.\textsuperscript{7} Contraction of the atria against closed mitral and tricuspid valves produces cannon A waves, which may be perceived as neck pounding.
- A "rapid fluttering in the chest" suggests a tachyarrhythmia. Gradual onset suggests sinus tachycardia. Sudden onset suggests supraventricular re-entrant tachycardia or atrial fibrillation.

Circumstances where palpitations occur

- Stressful situations, panic attacks
- Periods of catecholamine excess (exercise)
- Sudden positional changes

Associated symptoms

- Chest pain
- Syncope
- Vertigo or dizziness
- Nausea or diaphoresis

Past medical history

- Heart failure
- History of MI
- Arrhythmias
- Left ventricular hypertrophy
- Hyperthyroidism

Past psychiatric history

- Anxiety or panic attacks

Medications, substance abuse

- Theophylline
- Caffeine
- Alcohol
- Cocaine
- Amphetamine

Physical exam

- Pulse rate and rhythm
- Evidence of hyperthyroidism
- Heart murmur (mitral valve prolapse)
- Evidence of heart failure

Diagnostic tests

- Blood tests for thyroid function, hematocrit, theophylline level
- Chest radiograph or echocardiogram for evidence of heart failure


Common symptoms associated with panic attacks:

- Palpitations
- Trembling
- Nausea or abdominal distress
- Chills or hot flashes

Electrocardiographic Clues to the Cause of Palpitations

<table>
<thead>
<tr>
<th>ECG findings</th>
<th>Suggested cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short PR interval, δ waves</td>
<td>AV re-entrant tachycardia</td>
</tr>
<tr>
<td>P mitrale, atrial premature beats</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Ventricular premature beats</td>
<td>Ventricular tachycardia</td>
</tr>
<tr>
<td>Q waves</td>
<td>Ventricular premature beats</td>
</tr>
<tr>
<td></td>
<td>Ventricular tachycardia</td>
</tr>
</tbody>
</table>

Predictors of a Cardiac Etiology of Palpitations

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>2.6</td>
</tr>
<tr>
<td>Description of an irregular beat</td>
<td>3.2</td>
</tr>
<tr>
<td>History of heart disease</td>
<td>3.5</td>
</tr>
<tr>
<td>Duration of event &gt; 5 minutes</td>
<td>5.7</td>
</tr>
</tbody>
</table>

Patients at high risk for arrhythmia
- Myocardial scar from a prior infarction
- Idiopathic dilated cardiomyopathy
- Valvular stenosis or regurgitation
- Hypertrophic cardiomyopathy

These patients may benefit from a more aggressive work up.

Ambulatory ECG monitoring

Holter monitoring
- Provides continuous cardiac monitoring for 24–48 hours.
- The reported yield of ambulatory ECG monitoring in detection of symptomatic arrhythmias is between 13% and 69%.3
- The percentage of patients in whom Holter monitoring recorded an ECG during symptoms ranges between 2 and 35% in different studies; 48-hour monitoring was more effective than 12 and 24-hour monitoring.

Benefits of Holter monitoring
- Useful in identifying underlying etiology in patients with frequent palpitations.
- Not dependent on the patient’s ability to activate the device; therefore, the test of choice in patients with asymptomatic arrhythmias.

Limitations of Holter monitoring
- Limited value in patients with sporadic or infrequent symptoms, since palpitations may not occur during the conventional 24–48 hour monitoring period.
- There is poor correlation between symptoms experienced by the patient and abnormal electrical activity. Patients should keep a symptom diary while wearing the monitor.
- Historically, the diagnostic sensitivity of Holter monitoring has been falsely elevated because studies often included rhythms that were abnormal but asymptomatic.
Patient activated ambulatory monitors
- **Cardiac event recorders:** convert ECG data to an audio signal. The patient applies a credit card sized device to the chest wall when experiencing palpitations. Electrical activity is recorded prospectively for 30–60 seconds. Data are saved only when the patient activates the recorder. Following the event, the patient transmits the audio signals by telephone to a central station that reconstructs the electrical signal into a conventional ECG.
- **Continuous loop event recorders:** the most common type is worn on the belt, with two electrodes applied to the patient’s chest wall. When the patient activates the device, the recorder stores preceding and subsequent electrical activity. The time intervals captured (up to an hour) can be programmed based on the patient’s history.

**Events Detected by Continuous Loop Event Recorders**

<table>
<thead>
<tr>
<th>Event</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms</td>
<td>39%</td>
</tr>
<tr>
<td>Ventricular ectopy (isolated)</td>
<td>33%</td>
</tr>
<tr>
<td>Atrial ectopy (isolated)</td>
<td>26%</td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
<td>11%</td>
</tr>
<tr>
<td>Atrial fibrillation or flutter</td>
<td>10%</td>
</tr>
<tr>
<td>Sinus tachycardia</td>
<td>8%</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>4%</td>
</tr>
<tr>
<td>Other</td>
<td>4%</td>
</tr>
</tbody>
</table>

**Benefits of patient activated recorders**
- Useful for identifying the etiology of palpitations in patients with sporadic symptoms by providing prolonged surveillance.
- In a randomized crossover trial of 43 patients with palpitations referred for Holter monitoring, event recorders were twice as likely as 48-hour Holter monitoring to provide a diagnostic rhythm strip during symptoms. Loop recorders are able to capture the onset of the arrhythmia.
- Because the patient activates the monitor at the time of symptoms, cause and effect are well established.
- A prospective cohort study of 105 patients with palpitations referred for continuous loop event recorders suggested that the optimal monitoring period is two weeks. Eighty-three percent of patients made an initial transmission during the first two weeks of monitoring. Diagnostic yield and cost effectiveness were very low beyond this period.

**Limitations of patient activated recorders**
- Non-looping recorders are unable to capture the initiation of arrhythmias.
- Data are acquired only if the patient activates the monitor. Both require patient activation and therefore do not record arrhythmias that are asymptomatic or that cause loss of consciousness. (Auto triggered monitors are now available.)
Loop recorders can be uncomfortable, since patch electrodes need to be worn on the chest wall for two weeks.

A strategy for evaluating palpitations
* History, physical, EKG, and appropriate laboratory tests will identify the etiology of palpitations in close to half the patients.
* The remaining patients should be evaluated for anxiety and panic disorders.
* Ambulatory cardiac monitoring may reveal an etiology in patients with heart disease, palpitations lasting longer than five minutes, or irregular beats.
* Standard Holter monitors should be ordered for patients with frequent palpitations or who cannot be relied upon to activate an event recorder.
* Event monitors, if available, should be ordered for patients who are capable of activating them.
* In patients with persistent palpitations without a diagnosis despite ambulatory monitoring, electrophysiologic studies may be considered.

Electrophysiologic testing: the ACC/AHA guidelines

* Role of electrophysiologic studies (EPS) in patients with unexplained palpitations
  
  Class I: patients are likely to benefit from EPS
  * Patients with palpitations who have a pulse rate documented by medical personnel as inappropriately rapid and in whom ECG recordings fail to document the cause of the palpitations.
  * Patients with palpitations preceding a syncopal episode.

  Class II: opinion is divided
  * Patients with clinically significant palpitations, suspected to be of cardiac origin, in whom symptoms are sporadic and cannot be documented.
  * Studies are performed to determine the mechanisms of arrhythmias, direct or provide therapy, or assess prognosis.

  Class III: EPS is not warranted
  * Patients with palpitations documented to be due to extracardiac causes (for example, hyperthyroidism).

Role of EPS in patients with premature ventricular complexes, couplets, and non-sustained ventricular tachycardia

* Class I
  * None

* Class II
  * Patients with other risk factors for future arrhythmic events (low ejection fraction, positive signal averaged ECG, and non-sustained VT on ambulatory ECG recordings) in whom


Non-sustained ventricular tachycardia: ≥3 consecutive ventricular complexes that last <30 seconds and do not produce loss of consciousness
EPS will be used for further risk assessment and in guiding therapy in patients with inducible VT.

- Patients with highly symptomatic, uniform morphology premature ventricular complexes, couplets, and non-sustained VT who are considered potential candidates for catheter ablation.

Class III
- Asymptomatic or mildly symptomatic patients with premature ventricular complexes, couplets, and non-sustained VT without other risk factors for sustained arrhythmias.

**Treatment**

**Ventricular premature beats**
- Interest in treating asymptomatic or mildly symptomatic ventricular arrhythmias waned following publication of the results of the Cardiac Arrhythmia Suppression Trial (CAST)\(^\text{13}\) in 1991.

- Treatment consists of:
  - reassurance
  - correction of any magnesium or potassium abnormalities
  - for symptomatic relief, low dose \(\beta\) blockers are often prescribed, although there are no large studies assessing their efficacy in this situation.

**Arrhythmias**
- Patients with significant arrhythmias (ventricular tachycardia, supraventricular tachycardia, paradoxical atrial fibrillation or flutter) should be referred to a cardiology consultant for management and possible EPS to determine whether the arrhythmia is inducible and amenable to catheter ablation or antiarrhythmic medications.

**Prognosis**
- The short term prognosis of patients with normal cardiac function who present with palpitations is excellent.\(^2^,^3\)
- Kennedy et al. followed a cohort of 65 patients with palpitations for a mean of 7.5 years, with only one death.\(^14\)
- In the Pittsburgh study,\(^3\) the one year mortality rate was 1.6% and the one year stroke rate was 1.1%. Within the first year, 75% of patients had recurrent episodes of palpitations. At one year follow up, 89% reported that their health was the same or improved compared to that at enrollment.

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This chapter covers chronic renal insufficiency and interventions to slow its progression.


Based on parallels between cardiovascular disease and chronic renal disease progression, we have proposed a paradigm that cardiovascular disease and chronic renal disease are outcomes of the same underlying disorders.


Normal values

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>0.7–1.3 mg/dl</td>
</tr>
<tr>
<td>Blood urea nitrogen (BUN)</td>
<td>9–25 mg/dl</td>
</tr>
<tr>
<td>Urine output</td>
<td>1 ml/min (1.5 l/d)</td>
</tr>
</tbody>
</table>

Lab abnormalities in renal failure

Increased

- BUN and creatinine
- Potassium
- Hydrogen ions
- Magnesium

Continued
The Cockcroft-Gault formula

\[
\text{GFR in ml/min} = \frac{(140 - \text{age}) \times (\text{weight in kg}) \times 0.85 \text{ (for women)}}{72 \times \text{serum creatinine in mg/dl}}
\]

Creatinine clearance in ml/min

\[
\text{mg of creatinine in a 24-hour urine collection} \times 0.07
\]
\[
\text{serum creatinine in mg/dl}
\]

- Serum creatinine clearance systematically overestimates GFR. Although creatinine is cleared primarily by glomerular filtration, it is also secreted at the proximal tubule. Initially, a significant decline in GFR may not be reflected in increased serum creatinine. Thus, a patient with a GFR as low as 70 ml/min may have a misleadingly normal creatinine level.

- Levey et al.\(^6\) developed a more accurate prediction equation for GFR based on creatinine, age, sex, race, BUN, and albumin. It does not require a 24-hour urine collection but does require logarithms. The authors found that the Cockcroft-Gault creatinine clearance formula overestimates GFR by 16%.

GFR in ml/min

\[
170 \times [\text{Plasma creatinine in mg/dl}]^{-0.999} \times [\text{Age}]^{-0.176} \times 0.762 \text{ if the patient is female} \times 1.18 \text{ if the patient is black} \times [\text{blood urea nitrogen in mg/dl}]^{-0.170} \times [\text{serum albumin in g/dl}]^{0.318}
\]

Microalbuminuria and proteinuria

- Urine dipsticks lack the sensitivity to detect microalbuminuria (30–300 mg/day). A “trace” protein result obtained by reagent strip corresponds to protein excretion of 300–600 mg/day.

- Microalbuminuria, as evidenced by an elevated urinary albumin/creatinine ratio (UACR), can be diagnosed with a single tube of urine, preferably obtained in the early morning.\(^7\) This avoids a 24-hour collection, which is inconvenient for the patient and prone to collection errors.

\[
\begin{aligned}
\text{mg/day} & \quad \text{UACR in microgram/mg} \\
\text{Normal:} & \quad <30 \quad <30 \\
\text{Microalbuminuria:} & \quad 30–300 \quad 30–300 \\
\text{Proteinuria:} & \quad >300 \quad >300 \\
\text{Nephrotic range:} & \quad >3000–3500/day
\end{aligned}
\]

- A 24-hour urine for protein and creatinine should be obtained in patients with significant proteinuria. Proteinuria greater than 1 g per day calls for a tighter blood pressure target (125/75).

- Microalbuminuria is an indicator of increased risk of ESRD and an indication for ACE inhibitors, even in normotensive patients.
Proteinuria is a marker for cardiovascular morbidity and mortality in diabetic patients.

Blood tests for glomerulonephritis
- Serological blood tests prior to referral to a nephrologist can help with diagnosis.
- Complement levels: reduced total complement (CH50), C3, and C4 suggest postinfectious glomerulonephritis, membranoproliferative glomerulonephritis, lupus nephritis, cryoglobulinemia, or endocarditis.
- Hepatitis C antibody: a positive test suggests hepatitis C virus induced immune complex disease: membranoproliferative glomerulonephritis, membranous glomerulopathy, and cryoglobulinemia.
- Antineutrophil cytoplasmic antibodies (ANCA): highly sensitive and specific for Wegener’s granulomatosis.
- Antiglomerular basement membrane antibodies: a high titer is diagnostic of antiglomerular basement membrane nephritis; this is termed Goodpasture’s syndrome if the patient also has pulmonary hemorrhage.

Renal ultrasound
- Usually performed to exclude lower tract obstruction, polycystic kidney disease, and renal masses.
- Small kidneys (<8 cm) are strongly associated with irreversible sclerosis.

Indications for renal biopsy
- Renal biopsy should be performed when the results will affect therapy.8,9
- Nephrotic syndrome not caused by diabetic nephropathy, in order to distinguish between the major causes:
  —minimal change disease (responsive to steroids – the most treatable of the glomerulopathies)
  —membranous nephropathy
  —focal glomerulosclerosis (FGS).
- Lupus nephritis to distinguish between focal and diffuse proliferative disease.
- Rapidly progressive glomerulonephritis
- Suspected small vessel vasculitis: Wegener’s granulomatosis or microscopic polyarteritis nodosa. The presence of ANCAs is not sufficiently specific to initiate treatment.

Treatment
Slowing the progression of chronic renal insufficiency
- Glucose control in diabetic patients
- Blood pressure control
- ACE inhibition
- Low protein diet

Glucose control
- Without treatment, 75% of type 1s and 20% of type 2s with proteinuria >300 mg/day develop ESRD within 20 years.

Urinary albumin/creatinine ratio (UACR) conversion formula
1 microgram/mg = 1 mg/g = 0.11 g/mol
1 g/mol = 8.8 mg/g

Nephritis
- Hematuria
- Misshapen red blood cells
- Red blood cell casts
- Proteinuria

Nephrotic syndrome
- Proteinuria
- Decreased serum albumin
- Hyperlipidemia


<table>
<thead>
<tr>
<th>Indication</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrotic range</td>
<td>86</td>
</tr>
<tr>
<td>proteinuria</td>
<td></td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>71</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>45</td>
</tr>
<tr>
<td>Hematuria/proteinuria</td>
<td>32</td>
</tr>
<tr>
<td>Hematuria</td>
<td>3</td>
</tr>
</tbody>
</table>

Nephrotic syndrome in a diabetic patient can be assumed to be secondary to diabetic nephropathy, especially if retinopathy is also present.
• Diabetes is the primary cause of 40% of new ESRD cases.  
• In the Diabetes Control and Complications Trial, type 1 diabetic patients placed on intensive insulin treatment (3–4 shots per day or an insulin pump) had a 39% reduction in microalbuminuria (≥40 mg/day) and a 54% reduction in albuminuria (≥300 mg/day) compared with the conventional treatment group (1–2 shots per day).
• In the United Kingdom Prospective Diabetes Study of type 2 diabetic patients, intensive treatment reduced the risk of twofold increase in creatinine by 74% compared to conventional treatment at 12 years. Renal failure occurred in 16 of 2729 (0.6%) of intensive control patients versus nine of 1138 (0.8%) conventional treatment patients. This reduction was not significant.

Blood pressure control
• Hypertension is a strong independent risk factor for nephrosclerosis and endstage renal disease.
• Between 1973 and 1975, the Multiple Risk Factor Intervention Trial screened 332,544 men between 35 and 57 years of age and followed them through 1990.

MRFIT Results

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>Relative risk of ESRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;120/80</td>
<td>1</td>
</tr>
<tr>
<td>Stage 1 (140–159/90–99)</td>
<td>3.1</td>
</tr>
<tr>
<td>Stage 2 (160–179/100–109)</td>
<td>6.0</td>
</tr>
<tr>
<td>Stage 3 (180–209/110–119)</td>
<td>11.2</td>
</tr>
<tr>
<td>Stage 4 (≥210/≥120)</td>
<td>22.1</td>
</tr>
</tbody>
</table>

• The Modification of Diet in Renal Disease Study showed the beneficial effect of a tighter blood pressure target on the progression of renal dysfunction in patients with proteinuria.
• JNC-6 recommended a target blood pressure of <130/85 for patients with renal failure and <125/75 for patients with >1 gram per day proteinuria.
• ACE inhibitors slow the progression of diabetic and non-diabetic nephropathy and are the antihypertensive agents of choice in renal insufficiency.
• Diltiazem and verapamil (non-dihydropyridine calcium channel blockers) slow the progression of proteinuria almost as well as ACE inhibitors. The evidence is stronger in diabetic than in non-diabetic nephropathy. Trials of dihydropyridines (amlodipine, nifedipine, etc.) have shown varying effects on proteinuria.
• Thiazide diuretics lose their ability to lower blood pressure at creatinine levels >2.5 mg/dl. Loop diuretics, along with sodium restriction, should be used in this setting.

Angiotensin converting enzyme inhibition
• The antiproteinuric effect of ACE inhibitors is only partially due to blood pressure lowering. Blockade of the


13 Lazarus JM, Bourgoignie JJ, Buckalew VM et al. Achievement and safety of a low blood pressure goal in chronic renal disease. The Modification of Diet in Renal Disease Study Group. Hypertension 1997;29:641–50. 585 patients with renal failure (GFR 13–55 ml/min) were randomized to usual or low blood pressure targets. The tight control group attained a mean BP of 93.0 mmHg; the usual target group attained a BP of 97.7 mmHg. Each 1 mm Hg increase in follow up systolic BP was associated with a 1.35 times greater risk of hospitalization for cardiovascular or cerebrovascular disease. The authors recommended a mean arterial BP target of ≤92 mmHg, equivalent to 125/75.


effects of angiotensin II at the efferent arteriole dilates the vessel and reduces glomerular capillary pressure.

- ACE inhibitors can lower GFR and impair potassium excretion, especially when afferent blood supply is reduced by volume depletion or renal artery stenosis.\textsuperscript{16} They should be used with caution in patients with moderate or severe reduction in GFR.

- Angiotensin receptor blockers may be used in patients intolerant of ACE inhibitors. Studies of their long term effects on renal function are in progress.

**In diabetic nephropathy**
- The classic study of enalapril in type 1 diabetes by Lewis \textit{et al}\textsuperscript{17} showed a 50\% reduction in hard clinical endpoints at three years. Three quarters of the patients had hypertension (>140/90) at baseline.

- ACE inhibitors have been shown to slow the progression of proteinuria (a surrogate endpoint) in normotensive diabetic patients.

- A meta-analysis\textsuperscript{18} of normotensive type 1 diabetic patients with microalbuminuria showed that ACE inhibitors reduced progression to proteinuria and were capable of returning protein excretion to normal levels in some patients.

- There is less conclusive evidence of benefit in normotensive type 2 diabetic patients. Ravid \textit{et al}\textsuperscript{19} randomized 108 normotensive type 2 diabetic patients with microalbuminuria to enalapril or placebo. At five years, mean albuminuria increased in the placebo group from 123 to 310 mg/day but remained stable in the enalapril group.

**In non-diabetic nephropathy**
- The benefit of ACE inhibition in non-diabetic nephropathy is more difficult to ascertain. Although most renal disease is non-diabetic, the individual diseases (glomerulonephritis, polycystic disease, interstitial nephritis) are rare. The studies include myriad kidney diseases with different mechanisms; this heterogeneity complicates interpretation of the results.

- Maschio \textit{et al}\textsuperscript{20} reported a beneficial effect of the ACE inhibitor benazepril in primarily non-diabetic renal disease. They randomized 583 patients with mild to moderate renal insufficiency (creatinine clearance 30–60 ml/min) to benazepril or placebo. At three years, doubling of creatinine (2.1 mg/dl at baseline) or need for dialysis was experienced by 31/300 of the benazepril group versus 57/283 of the placebo group (NNT = 11). The mortality increase in the benazepril group was thought to be a chance occurrence (P = 0.04).

- In a meta-analysis of 10 trials\textsuperscript{21} comparing ACE inhibitors to other antihypertensive agents in non-diabetic patients, ESRD occurred in 52/806 (6.4\%) of ACE inhibitor patients and 72/788 (9.1\%) of controls (RRR = 0.30, ARR = 2.7\%, NNT = 37). There was no significant difference in mortality between the two groups.

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\textsuperscript{16} Textor SC. Renal failure related to angiotensin-converting enzyme inhibitors. Semin Nephrol 1997;17:67–76.

\textsuperscript{17} Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of ACE inhibition on diabetic nephropathy. N Engl J Med 1993;329:1456–62. 409 type 1 diabetic patients with >500 mg/day proteinuria and creatinine <2.5 mg/dl were randomized to captopril or placebo. 23/207 captopril patients v 42/202 placebo patients experienced death, dialysis, or transplantation at a median follow up of three years (RRR = 50\%, ARR = 9.7\%, NNT = 10). Risk reduction was greater for patients with higher creatinine levels.


- Glomerulopathy 33\%
- Interstitial nephritis 18\%
- Nephrosclerosis 17\%
- Polycystic kidney disease 11\%
- Diabetic nephropathy 4\%
- Miscellaneous or unknown 18\%

Low protein diet

- The Modification of Diet in Renal Disease Study is the most important trial to date of protein restriction. There was no difference in GFR decline seen in Study A, in which low protein diets (0.58 g/kg/d) or usual protein diets (1.3 g/kg/d) were given to 585 patients with moderate renal insufficiency (GFR 25–55 ml/min/1.73 m² of body surface).
- In Study B, 255 patients with severe renal insufficiency (GFR 13–24) were randomized to low or very low (0.28 g/kg/d) protein diets. Although the initial 1994 study failed to demonstrate conclusive benefit, a secondary analysis of the Study B patients showed that a 0.2 g/kg/d reduction in protein intake was associated with a 1.15 ml/min/y slower mean decline in GFR, equivalent to a 29% reduction. Keto acid amino acid supplementation did not affect GFR decline.
- A meta-analysis found that, in 1413 non-diabetic patients pooled from five trials, a protein restricted diet (PRD) was associated with a 33% reduction in the risk of renal failure or death compared with a usual protein diet.
- In 108 type 1 diabetic patients pooled from five trials, PRD was associated with a 44% reduction in GFR or increase in albuminuria (surrogate markers of renal disease progression). The benefits of PRD were independent of blood pressure or glucose control.
- Low protein diets are controversial because of concerns about their nutritional adequacy. While protein restriction can preserve GFR and delay dialysis, malnutrition at the initiation of dialysis is associated with increased mortality. Some clinicians favor early initiation of dialysis instead of low protein diets.
- Adherence to low protein diets is a major problem. Even in supervised clinical trials, compliance has been suboptimal. (See sample menu at right.)
- Low protein diets (0.6 g/kg/d) may be considered for patients with severe renal insufficiency (GFR < 25 ml/min).

Special treatment issues

Anemia

- Patients with substantially decreased GFR should be evaluated for anemia if:
  - hematocrit is < 33% in a premenopausal woman
  - hematocrit is < 37% in a man or a postmenopausal woman.
- Anemia evaluation consists of:
  - reticulocyte count
  - fecal occult blood testing
  - ferritin, iron, and iron binding capacity.
- The effectiveness of human recombinant erythropoietin in the therapy of renal anemia is well established.
- Erythropoietin deficiency can be assumed to be the cause of anemia in moderate or severe renal insufficiency when there is no other etiology. Erythropoietin levels are not routinely indicated.

Sample 0.6 g protein/kg diet for a large person (100 kg)
60 g protein/1.1 g sodium/2258 calories

Breakfast
- Apple juice (1/2 cup)
- Shredded wheat (3/4 cup) with whole milk (1/2 cup) and 2 teaspoons of sugar
- 1 hard-boiled egg (3 times a week)

Lunch
- Salisbury steak (2 oz) with gravy (1 tablespoon)
- Seasoned noodles (1/2 cup)
- Carrots (1/2 cup)
- Apple

Dinner
- Broiled chicken (2 oz)
- Rice (1/2 cup)
- Green beans (1/2 cup)
- Canned pears (1/2 cup)
- 1 slice of whole wheat toast with margarine, and coffee or tea with sugar are permitted at every meal.

References
27 Marsh WA, Rascati KL. Meta-analyses of the effectiveness of erythropoietin for end-stage renal disease and cancer. The effectiveness of erythropoietin in ESRD was 87%. Effectiveness was defined as an increase of 6 points in hematocrit or 2 g/dl in hemoglobin.
Adequate iron stores are essential for successful erythropoietin therapy.

Serum ferritin measures iron stored in the liver, spleen, and bone marrow. Target ferritin in the setting of renal insufficiency is 100 ng/ml. Patients who fail to meet target despite being compliant with oral ferrous sulfate 325 mg three times a day should receive intramuscular iron injections.

Transferrin saturation or iron/total iron binding capacity (Fe/TIBC) indicates the supply of iron available for hematopoiesis. Target transferrin saturation is ≥20%.

Several multicenter studies are under way to determine the optimal hemoglobin level in patients with renal insufficiency. In hemodialysis patients, hematocrit levels <30% have been associated with a decline in left ventricular function, cognition, and quality of life. Based on opinion, practice guidelines recommend a target hematocrit of 33–36% (hemoglobin 11–12 g/dl).

The initial erythropoietin dose is 80–120 units per kilogram (typically 6000 units) given subcutaneously in 2–3 doses per week.

Hematocrit usually increases by about one percentage point per week. Target should be reached in 2–4 months.

If the rate of rise in hematocrit is too slow (<1.5 percentage points in 1 month), the dose should be increased by 25–50%. If the rate of rise is too fast (>3 percentage points in two weeks) the dose should be reduced by 25%.

Hematocrit should be monitored every 1–2 weeks when beginning therapy or changing doses. When hematocrit has stabilized, every 2–4 months is sufficient.

Metabolic Acidosis

There are no definitive studies on the management of metabolic acidosis in chronic renal failure.

Traditionally the absolute indications for alkali therapy in asymptomatic patients with acidosis have been:

—$\text{HCO}_3^-$ < 12 meq/l
—hyperkalemia.

However, more aggressive treatment with sodium bicarbonate may retard the development of osteopenia, skeletal muscle breakdown, and tubulointerstitial damage.

Plasma bicarbonate should be maintained at a level >20 meq/l with sodium bicarbonate ~2 g/day. Sodium citrate (Shohl’s solution) should be avoided because citrate may contribute to aluminum intoxication, especially when used with aluminum-containing drugs (Maalox, Amphojel).

Excessive use of sodium bicarbonate can result in volume overload, alkalosis, and calcium phosphate kidney stones.

Edema

Loop diuretics should be used at creatinine levels ≥2.5 mg/dl.

In refractory edema, loop diuretics may be administered more than once a day or combined with diuretics that have

NSAIDs in renal failure

The most common side effect of NSAIDs is an acute, reversible reduction in GFR due to blockade of vasodilating prostaglandins. It is especially likely to occur in patients with low flow states like heart failure and volume depletion. Acetaminophen is the analgesic of choice when GFR is <50 ml/min. Murray MD, Brater DC. Renal toxicity of the nonsteroidal anti-inflammatory drugs. Ann Rev Pharmacol Toxicol 1993;33:433–65.

Antacids in renal failure

- Antacids containing aluminum (Maalox, Mylanta, Amphojel) or citrate (Alka-Seltzer, Bromo-Seltzer) are not ideal because of possible aluminum toxicity.
- Antacids containing magnesium (Maalox, Mylanta) can worsen hypermagnesemia.
- $\text{H}_2$ blockers require dose adjustment (see Table 33.2).
- Proton pump inhibitors can be given at the usual dosages.

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Edema

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One gram of sodium bicarbonate provides 11.9 mEq of sodium and bicarbonate. The sodium load can be hazardous to patients with volume overload.
their effect on different parts of the nephron (for example, metolazone).

Renal osteodystrophy/secondary hyperparathyroidism
Pathophysiology
- Renal osteodystrophy includes osteitis fibrosa (a high turnover state) and osteomalacia/adynamic bone disease (low turnover states). There is overlap between the diseases. Definitive diagnosis requires bone biopsy, which is rarely done.
- Although the mechanism is complex and multifactorial, the high turnover mechanism of osteitis fibrosa is well established.
  - Low levels of 1α,25-dihydroxyvitamin D₃ impair the conversion of 25-hydroxyvitamin D₃ to the active 1,25-dihydroxyvitamin D₃. Deficiency of active vitamin D₃ causes decreased intestinal absorption of calcium.
  - Hypocalcemia causes secondary hyperparathyroidism, with increased osteoclastic and osteoblastic activity and consequent destruction of bone.
- The low turnover states of osteomalacia and adynamic bone disease are now thought to be due more to aluminum toxicity than pure vitamin D deficiency.
- The goals of treatment are to:
  - maintain normal levels of serum calcium and phosphorus
  - correct vitamin D deficiency
  - suppress parathyroid hormone secretion.

Hypocalcemia and hyperphosphatemia
- Supplementation with calcium carbonate or acetate treats both problems.
- Serum calcium levels should be maintained at the high end of the normal range in order to prevent hyperparathyroidism, provided that the patient’s phosphate is controlled. A calcium-phosphate product >70 suggests the risk of kidney stones and metastatic calcification.
- The patient should eat a low phosphate diet.

Vitamin D analogs
- Raise calcium levels by improving the intestinal absorption of calcium.
- Calcitriol is the most potent suppressor of parathyroid hormone (PTH) secretion.
- The vitamin D analogs may cause hypercalcemia. Calcium levels should be followed.
- Paricalcitol (Zemplar) is one of a new class of vitamin D analogs that suppresses PTH without raising calcium levels.
- To maintain bone formation and remodeling, the generally accepted target range for iPTH is ≤1.5–3 times the upper limit of normal.

Uremia
Symptoms
- Fatigue, weakness
- Pruritus
- Easy bruising
- Metallic taste in mouth
- Dyspnea on exertion
- Chest pain on inspiration
- Nausea, vomiting
- Leg cramps and numbness
- Irritability, loss of concentration

Signs
- Pallor
- Rales, pleural effusion, edema
- Friction rub
- Confusion, asterixis, myoclonus
- Bruises, excoriation, dry skin
- Isosthenuria (specific gravity 1.010)

Vitamin D supplements and analogs
- Ergocalciferol D₂
- Cholecalciferol D₃
- Calcifediol 25(OH)D₃
- Calcitriol 1,25(OH)₂D₃
- Dihydrotachysterol
- Paricalcitol

Calcium-phosphorus product
Serum Ca (mg/dl) × serum P (mg/dl)

Baker LR Abrams, Roe CJ et al. 1,25(OH)₂D₃ administration in moderate renal failure: a prospective double blind trial. Kidney Int 1989; 35:661. A small study of 16 patients with creatinine clearances of 20–59 ml/min and no radiographic evidence of bone disease. At 12 months, calcitriol 0.25–0.5 microgram PO qd lowered serum phosphorus and alkaline phosphatase levels compared to placebo. Improvement was also seen in the histological changes of hyperparathyroidism. Despite the normal radiographs, bone biopsies were abnormal in all patients.
Folic acid
- Elevated homocysteine levels have been implicated as a factor in the marked increase in cardiovascular death seen in patients with chronic renal failure.
- In predialysis patients, folate supplementation has been shown to reduce homocysteine levels, a surrogate marker for cardiovascular disease.\(^{30}\)

Dialysis
Indications for dialysis
- Hyperkalemia refractory to conservative measures
- Fluid overload refractory to diuretics
- Acidosis refractory to alkali therapy
- Uremia
- Bleeding diathesis related to uremia
- Malnutrition at initiation of dialysis is associated with decreased survival.\(^{31}\)
- Evidence of malnutrition:
  - weight loss
  - albumin < 4.0 g/dl (when not caused by nephrotic syndrome)
  - transferrin (TIBC) < 200 mg/dl
  - protein intake < 0.8 g/kg/d.
- There is evidence from cohort and case control studies that early referral for dialysis before the standard indications have developed results in better outcomes than late referral.\(^{32}\)

Preparation for endstage renal failure
- The prospect of dialysis is profoundly disturbing to most patients. Social and psychological preparation by a multidisciplinary team can ease the transition.
- The main decisions to be made are:
  - Hemodialysis v peritoneal dialysis v transplantation
  - A-V fistula v prosthetic graft for hemodialysis.

Hemodialysis
- A surgically created arteriovenous fistula requires at least six weeks before it can be used; therefore, access for long term hemodialysis should be created when serum GFR goes below 20 ml/min.
- A native cephalic vein to radial artery fistula is the preferred form of access, with a two year survival rate of >75%.
- Prosthetic graft placement has a two year complication free survival rate of only 30%.
- For urgent dialysis, a double lumen catheter placed in the femoral or internal jugular vein can be used.
- Patients usually go to a hemodialysis center three times a week. Each session takes 3–4 hours.


Save veins! No phlebotomy or intravenous lines in the non-dominant arm of a patient who will probably require dialysis.
Peritoneal dialysis
- Accounts for only ~10% of dialysis in the US.
- Dialysis solution is infused into the peritoneal cavity through a catheter and remains there for several hours.
- PD is attractive to patients because it is less disruptive to lifestyle than thrice weekly hemodialysis. PD can be done by the patient at home or at work.
- PD is best suited to younger patients with good eyesight and manual dexterity who wish to maintain autonomy and independence.
- A PD catheter can be used shortly after placement.
- The most common continuous ambulatory peritoneal dialysis (CAPD) protocol uses four daily 2l exchanges.
- In continuous cyclic peritoneal dialysis (CCPD), an automated cycler infuses and drains dialysis fluid overnight. A 1994 Dutch study\textsuperscript{33} found that CAPD provided equivalent dialysis adequacy with fewer hospitalizations and less peritonitis than CCPD. The two methods may be used together.

Kidney transplantation
- As of February 24, 2001, there were 47,996 patients awaiting cadaveric kidney transplantation.\textsuperscript{3}
- The average waiting time for a cadaveric donor kidney is ~4 years; the wait is highly influenced by level of sensitization (blood type and HLA antigens).
- Each person has six HLA antigens: two A, two B, and two DR. The best match is a kidney from a living HLA identical sibling (10 year graft survival 74%); the worst match is a cadaver kidney with five or six HLA mismatches (10 year graft survival 34%).
- Kidneys from living donors are available immediately. Increasingly, spouses and friends are being accepted as living donors. About 45% of transplanted kidneys come from living donors.

Patient Survival (%)\textsuperscript{1}

<table>
<thead>
<tr>
<th>Survival Period</th>
<th>Dialysis</th>
<th>Cadaveric</th>
<th>Living related donor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year (1997–8)</td>
<td>79.7</td>
<td>94.4</td>
<td>97.5</td>
</tr>
<tr>
<td>2 years (1996–8)</td>
<td>65.6</td>
<td>91.8</td>
<td>96.2</td>
</tr>
<tr>
<td>5 years (1993–8)</td>
<td>29.0</td>
<td>79.5</td>
<td>89.1</td>
</tr>
<tr>
<td>10 years (1988–98)</td>
<td>8.4</td>
<td>56.5</td>
<td>77.4</td>
</tr>
</tbody>
</table>

Some contraindications to transplantation
- Expected lifespan < 5 years
- Age over 70
- Cancer or advanced cardiopulmonary disease
- Psychiatric problems
- Active infection
- Active glomerulonephritis

Summary

Early interventions
- Blood pressure target of 130/85 for patients with reduced GFR
- Blood pressure target of 125/75 for proteinuria > 1 g/day
- Aggressive glucose control in diabetic patients
- ACE inhibitors for diabetic patients with microalbuminuria (UACR > 20), even if blood pressure is at target (≤ 130/85)
- Careful attention to cardiovascular disease
- Referral to a nephrologist at a creatinine level ≥ 2.0 mg/dl

Later interventions
- Careful monitoring of GFR, hematocrit, iron stores, potassium, calcium, phosphate, acid–base status
- Erythropoietin to maintain hematocrit at 30–36%; iron supplementation to maintain ferritin ≥ 100 mg/dl and transferrin saturation ≥ 20%.
- Consider a low protein diet (<0.6 g/kg/d) at a GFR < 25 ml/min.
- Calcium carbonate or acetate to maintain calcium at > 8.0 mg/dl, and phosphorus < 4.5 mg/dl.
- Sodium bicarbonate to maintain plasma HCO₃⁻ > 20 meq/l.
- Counseling about chronic renal replacement therapy: hemodialysis, peritoneal dialysis, transplantation.
- Hemodialysis access when GFR is < 20 ml/min.
Table 33.1  Agents for chronic renal insufficiency.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage forms (mg)</th>
<th>Usual dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACE inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enalapril (Vasotec)</td>
<td>2.5/5/10/20</td>
<td>2.5–20 mg PO bid</td>
<td>Acute renal failure, especially in patients with creatinine</td>
</tr>
<tr>
<td>Captopril (Capoten)</td>
<td>12.5/25/50</td>
<td>6.25–100 mg PO tid</td>
<td></td>
</tr>
<tr>
<td>Lisinopril (Prinivil, Zestril)</td>
<td>2.5/5/10/20/40</td>
<td>2.5–40 mg PO qd</td>
<td>&gt; 3.0, renal artery stenosis, or volume depletion</td>
</tr>
<tr>
<td>Ramipril (Altace)</td>
<td>1.25/2.5/5/10</td>
<td>1.25–10 mg PO qd</td>
<td></td>
</tr>
<tr>
<td><strong>Angiotensin receptor blockers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan (Atacand)</td>
<td>4/8/16/32</td>
<td>8–32 mg PO qd</td>
<td></td>
</tr>
<tr>
<td>Losartan (Cozaar)</td>
<td>25/50/100</td>
<td>25–100 mg PO qd</td>
<td></td>
</tr>
<tr>
<td>Valsartan (Diovan)</td>
<td>80/160</td>
<td>80–320 mg PO qd</td>
<td></td>
</tr>
<tr>
<td><strong>Diuretics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrochlorothiazide (EsiDrix, HydroDiuril)</td>
<td>25/50/100</td>
<td>25–50 mg PO qd</td>
<td>Ineffective at GFR &lt; 30 ml/min</td>
</tr>
<tr>
<td>Furosemide (Lasix)</td>
<td>20/40/80</td>
<td>20–80 mg PO qd</td>
<td>Azotemia, volume depletion</td>
</tr>
<tr>
<td>Metolazone (Zaroxolyn)</td>
<td>2.5/5/10</td>
<td>2.5–10 mg PO qd</td>
<td>Used with furosemide</td>
</tr>
<tr>
<td><strong>Calcium Channel Blockers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diltiazem (Tiazac)</td>
<td>120/180/240/300/360/420</td>
<td>120–420 mg PO qd</td>
<td></td>
</tr>
<tr>
<td>Verapamil (Calan SR)</td>
<td>120/180/240</td>
<td>120–240 mg PO qd</td>
<td></td>
</tr>
<tr>
<td><strong>Erythropoietin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procrit, Epogen</td>
<td>2000–20 000 U/ml 1 ml vials</td>
<td>80–120 U/kg SC 2–3 times/week</td>
<td>Hypertension, Titrate dose to hematocrit</td>
</tr>
<tr>
<td><strong>Iron</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferrous sulfate</td>
<td>325</td>
<td>325 mg PO tid</td>
<td>Injectable into the buttock with a 2-inch 20 G needle. Titrate dose to hematocrit and weight</td>
</tr>
<tr>
<td>Iron dextran (INFeD)</td>
<td>50 mg/ml 2 ml vials</td>
<td>100 mg IM qd</td>
<td></td>
</tr>
<tr>
<td><strong>Calcium supplements/ phosphate binders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium acetate (Phos-Lo)</td>
<td>667 mg (169 mg Ca) 1.5 g (600 mg Ca)</td>
<td>667 mg PO qd 1.5 g PO qd</td>
<td>Metastatic calcification when [calcium] x [phosphorus] &gt; 70</td>
</tr>
<tr>
<td><strong>Vitamin D</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcitriol (Rocaltrol)</td>
<td>0.25/0.5 microgram</td>
<td>0.25 microgram PO qd</td>
<td></td>
</tr>
<tr>
<td><strong>Alkali</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>325/650</td>
<td>650 mg PO tid</td>
<td>Max. dose: 15 g in patients &lt; 60, 8 g in patients ≥ 60</td>
</tr>
<tr>
<td><strong>Vitamins</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephro-Vite Plus Iron (B complex, C, folate, d-biotin, folate)</td>
<td>1 tab PO qd</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Folic acid</td>
<td>1.0</td>
<td>1 mg PO qd</td>
<td></td>
</tr>
</tbody>
</table>
Table 33.2  Some common outpatient medications that require renal dosing*.

<table>
<thead>
<tr>
<th>Glomerular filtration rate</th>
<th>&gt;50 ml/min</th>
<th>10–50 ml/min</th>
<th>&lt;10 ml/min</th>
</tr>
</thead>
</table>

**ACE Inhibitors**

<table>
<thead>
<tr>
<th>Medication</th>
<th>&gt;50 ml/min</th>
<th>10–50 ml/min</th>
<th>&lt;10 ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benazepril</td>
<td>100%</td>
<td>50–75%</td>
<td>25–50%</td>
</tr>
<tr>
<td>Captopril</td>
<td>100%</td>
<td>75%</td>
<td>50%</td>
</tr>
<tr>
<td>Enalapril</td>
<td>100%</td>
<td>75–100%</td>
<td>50%</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>100%</td>
<td>100%</td>
<td>75–100%</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>100%</td>
<td>50–75%</td>
<td>25–50%</td>
</tr>
<tr>
<td>Quinapril</td>
<td>100%</td>
<td>75–100%</td>
<td>75%</td>
</tr>
<tr>
<td>Ramipril</td>
<td>100%</td>
<td>50–75%</td>
<td>25–50%</td>
</tr>
</tbody>
</table>

**Analgesics**

<table>
<thead>
<tr>
<th>Medication</th>
<th>&gt;50 ml/min</th>
<th>10–50 ml/min</th>
<th>&lt;10 ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>100%</td>
<td>75%</td>
<td>50%</td>
</tr>
<tr>
<td>Morphine</td>
<td>100%</td>
<td>75%</td>
<td>50%</td>
</tr>
</tbody>
</table>

**Antibiotics**

<table>
<thead>
<tr>
<th>Category</th>
<th>Medication</th>
<th>&gt;50 ml/min</th>
<th>10–50 ml/min</th>
<th>&lt;10 ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalosporins</td>
<td>See individual agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillins</td>
<td>See individual agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinolones</td>
<td>See individual agents</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**B-blockers**

<table>
<thead>
<tr>
<th>Medication</th>
<th>&gt;50 ml/min</th>
<th>10–50 ml/min</th>
<th>&lt;10 ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>100%</td>
<td>50%</td>
<td>30–50%</td>
</tr>
<tr>
<td>Atenolol</td>
<td>100%</td>
<td>50%</td>
<td>30–50%</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>100%</td>
<td>50%</td>
<td>30–50%</td>
</tr>
<tr>
<td>Propranolol</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Diabetes drugs**

<table>
<thead>
<tr>
<th>Medication</th>
<th>&gt;50 ml/min</th>
<th>10–50 ml/min</th>
<th>&lt;10 ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acarbose</td>
<td>50–100%</td>
<td>Avoid</td>
<td>Avoid</td>
</tr>
<tr>
<td>Insulin</td>
<td>100%</td>
<td>75%</td>
<td>50%</td>
</tr>
<tr>
<td>Metformin</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Avoid</td>
</tr>
<tr>
<td>Glipizide</td>
<td>100%</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Glyburide</td>
<td>No data</td>
<td>Avoid</td>
<td>Avoid</td>
</tr>
</tbody>
</table>

**Diuretics**

<table>
<thead>
<tr>
<th>Medication</th>
<th>&gt;50 ml/min</th>
<th>10–50 ml/min</th>
<th>&lt;10 ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrochlorothiazide</td>
<td>Ineffective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>q6–12h</td>
<td>q12–24h</td>
<td>Avoid</td>
</tr>
<tr>
<td>Triamterene</td>
<td>q12h</td>
<td>q12h</td>
<td>Avoid</td>
</tr>
</tbody>
</table>

**H2 blockers**

<table>
<thead>
<tr>
<th>Medication</th>
<th>&gt;50 ml/min</th>
<th>10–50 ml/min</th>
<th>&lt;10 ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine</td>
<td>100%</td>
<td>50%</td>
<td>25%</td>
</tr>
<tr>
<td>Famotidine</td>
<td>50%</td>
<td>25%</td>
<td>10%</td>
</tr>
<tr>
<td>Nizatidine</td>
<td>75%</td>
<td>50%</td>
<td>25%</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>75%</td>
<td>50%</td>
<td>25%</td>
</tr>
</tbody>
</table>

**Other**

<table>
<thead>
<tr>
<th>Medication</th>
<th>&gt;50 ml/min</th>
<th>10–50 ml/min</th>
<th>&lt;10 ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopurinol</td>
<td>75%</td>
<td>50%</td>
<td>25%</td>
</tr>
<tr>
<td>Digoxin</td>
<td>100%</td>
<td>100%</td>
<td>50–75%</td>
</tr>
<tr>
<td>Methadone</td>
<td>100%</td>
<td>100%</td>
<td>50–75%</td>
</tr>
<tr>
<td>Niacin</td>
<td>100%</td>
<td>50%</td>
<td>25%</td>
</tr>
</tbody>
</table>

Seizure disorders

34

Sandra Kammerman

Epidemiology
- Seizures are the most common acute neurologic problem in the United States.
- Epilepsy (recurrent seizures) is the third most common serious neurologic disorder, following stroke and Alzheimer’s disease.
- The age adjusted incidence of newly diagnosed epilepsy is 44/100,000 person years. The incidence of epilepsy increases with advanced age; people over 75 are twice as likely to develop new onset epilepsy as all adult age groups under 65.1
- By age 74, 3% of all people will have had epilepsy at some point in their lives. For those living to 85, the cumulative incidence rises to 4.4%.1
- The prevalence of active epilepsy is 0.68%. The prevalence of all unprovoked seizures (including epilepsy) is 0.82%.2

Classification of seizures3,4
Partial (focal) seizures
- These account for almost 60% of new cases of epilepsy.2
- They begin locally, but can generalize.
- Simple partial seizures
  —Consciousness is not impaired.
  —Symptoms may be motor, cognitive, sensory, autonomic, or affective, depending on the area of cerebral cortex involved.
  —Occur in about 15% of patients with seizures.
- Complex partial seizures
  —Consciousness is partially or completely impaired, but there is no initial generalized tonic clonic activity.
  —The patient has no memory of the events during the seizure.
  —These occur in approximately 35% of patients with seizures.
  —There is usually an aura, automatism, postictal confusion, or tiredness. The presentation is extremely variable.
  —Also known as temporal lobe or psychomotor seizures.
- Partial seizures evolving to generalized seizures

Generalized seizures
- Seizures in which initial manifestations indicate involvement of both hemispheres, most commonly impairment of consciousness with bilateral motor involvement.
  —These account for 40% of patients with epilepsy.2
  —Patients usually forget all the events of the seizure.
- Absence (petit mal) seizures occur in 5% of all seizure patients, primarily in children. These patients typically present with staring or eye flickering; there are no convulsions or postictal symptoms. An atypical absence seizure may occur with some body movements.

Terminology
- Seizure: an uncontrolled, paroxysmal neuronal discharge in any part of the brain; it may cause physical or mental symptoms and may be convulsive or non-convulsive.
- Convulsion: involuntary contraction of body muscles
- Epilepsy: two or more unprovoked, recurrent seizures. Seventy-five percent of epilepsy is primary (idiopathic); 25% is secondary to another CNS disorder.1
- Simple seizure: no alteration of consciousness
- Complex seizure: alteration of consciousness
- Status epilepticus: epileptic seizures that are so frequent or prolonged as to create a fixed or lasting condition
SEIZURE DISORDERS

- **Myoclonic seizures** present with (usually) symmetric jerking of the extremities.
- **Clonic seizures** present with rapid, repetitive motor activity.
- **Tonic seizures** primarily present with rigidity.
- **Tonic clonic (grand mal) seizures** occur in 25% of all seizure patients and are the most common type of generalized seizure in adults. These begin with tonic stiffening (extension), followed by clonic flexion motions. Tonic clonic seizures may produce labored respirations, cyanosis, incontinence, involuntary tongue biting (a sign that is not sensitive but is specific), and postictal confusion, fatigue, or stupor.
- **Atonic seizures** present with a sudden loss of postural tone.

Distinguishing secondarily generalized partial seizures from primary generalized seizures

Many patients with partial seizures that generalize incorrectly report their seizures as “grand mal”. Distinguishing factors favoring secondarily generalized partial seizures are as follows.

- An aura preceding the seizure
- A period before the seizure when the patient is unresponsive and staring
  - Focal motor phenomena preceding the seizure
  - Automatisms preceding the seizure
  - Past occurrence of any of the above factors without impairment of consciousness
  - Focal findings on the neurologic exam
  - Focal activity on the electroencephalogram (EEG)
  - Focal finding on MRI
  - Adult onset of seizures

**Diagnosis**

**Introduction**

- Diagnosis and classification are made by history and sometimes corroborated by EEG.
- Reports from eyewitnesses are helpful.
- CT, MRI, and lab tests may be helpful in determining the cause, although approximately 75% of seizures are idiopathic.
- Diagnostic classification is necessary for appropriate therapy.

**Evaluation of a first idiopathic seizure**

- Classify according to categories above based upon available history.
- Consider etiology; systemic diseases that may cause seizures include renal failure, hepatic failure, systemic lupus erythematosus, AIDS, and porphyria.

**The most common etiologies by age**

- Ages 15 to 34: 85% idiopathic, 5% post traumatic, 3% congenital, 3% tumor

---

**Epilepsy in ancient Babylon**

“If at the time of his fit he loses consciousness and foam comes from his mouth it is *miqtu* (the falling disease: epilepsy).”

“If a death-wail sounds forth from him and (at each wail) he himself responds to it, rising and falling onto his knees, a demon from the desert has possessed him.”


**Epilepsy in the Gospels**

Here too epilepsy is explained as possession by demons. “When the spirit seizes him, the patient suddenly cries out, falls to the ground, foaming, and grinding the teeth.” *Luke 9:39.*

**Causes of non-epileptic seizures**

- Alcohol withdrawal
- Benzodiazepine withdrawal
- Massive sleep deprivation
- Excessive use of stimulants
- Psychogenic (conversion disorder, somatization, factitious disorder, malingering)
- Acute head trauma (within one week)
- CNS infection or neoplasm
- Uremia
- Eclampsia
- High fever
- Hypoxemia
- Hyper- or hypoglycemia
- Electrolyte disorders

Neurocysticercosis and malaria are two of the most common causes of seizures worldwide and should be considered in patients from high risk areas.

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• Ages 35 to 64: 60% idiopathic, 15% cerebrovascular, 7% post traumatic, 7% tumor
• Age over 65: 50% idiopathic, 30% cerebrovascular, 10% degenerative, 4% post traumatic

Electroencephalography (EEG)
• Establishes the diagnosis of epilepsy.
• Determines whether there is a localized focus of epileptiform activity.
• The standard 21 lead, 30 minute recording may be falsely negative; it has a sensitivity of only 50–60%. A 24 hour EEG may be necessary for diagnosis.

Other testing
• Blood tests: glucose, sodium, calcium, magnesium
• CT of the head with contrast: particularly useful in the setting of a focal seizure, neurologic deficit, or possible trauma.
• MRI of the head is indicated following a tonic clonic seizure. MRI will be positive in 10–20% of patients with a generalized tonic clonic seizure and a negative CT scan.
• Lumbar puncture is indicated only if infection or hemorrhage is suspected.

Evaluation for common precipitants
• Emotional stress
• Hyperventilation
• Menstrual cycle
• Sleep deprivation
• Alcohol withdrawal or excess
• Photic stimulation (strobe lights, television)
• Febrile seizures are very rare in adults.

Estimating risk of recurrent seizure
In untreated patients, recurrence after a first seizure occurs in 64% at six months, 70% at one year, and 81% at three years.

Recurrence Rate in Specific Subgroups after First Seizure

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>6 months (%)</th>
<th>1 year (%)</th>
<th>3 years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure after an acute insult</td>
<td>33</td>
<td>40</td>
<td>46</td>
</tr>
<tr>
<td>Seizure after a remote insult</td>
<td>70</td>
<td>75</td>
<td>85</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>62</td>
<td>69</td>
<td>81</td>
</tr>
<tr>
<td>Vascular process</td>
<td>66</td>
<td>73</td>
<td>82</td>
</tr>
<tr>
<td>Tumor</td>
<td>83</td>
<td>83</td>
<td>100</td>
</tr>
<tr>
<td>Alcohol</td>
<td>41</td>
<td>48</td>
<td>55</td>
</tr>
<tr>
<td>Tonic clonic</td>
<td>53</td>
<td>60</td>
<td>72</td>
</tr>
<tr>
<td>Partial</td>
<td>82</td>
<td>89</td>
<td>94</td>
</tr>
</tbody>
</table>

Psychosocial considerations in epileptology
• Health-related quality of life scores are significantly lower in patients with epilepsy than in the general public. Seizure


Classification of Epilepsy Syndrome Based Upon Clinical, EEG, and Neuroimaging Data

<table>
<thead>
<tr>
<th>Clinical + EEG</th>
<th>Clinical + MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized</td>
<td>8%</td>
</tr>
<tr>
<td>Partial</td>
<td>39%</td>
</tr>
<tr>
<td>Unclassified</td>
<td>53%</td>
</tr>
</tbody>
</table>

Early EEG, sleep deprived EEG and MRI after presentation at first seizure help to categorize seizures that cannot be classified based on clinical information alone.


Hart YM, Sander JWAS, Johnson AL, Shorvon SD. National General Practice Study of Epilepsy: recurrence after a first seizure. Lancet 1990;336:1271–4. This community based, observational study of 564 patients included patients who had their first seizure before the study began, as well as patients who entered the study at the time of their first seizure. Subgroup analysis of patients who were only assessed prospectively revealed a recurrence rate of 43% at two years.

frequency is a good predictor of quality of life; patients with no recurrences score close to the general public, but performance declines as seizure frequency rises.

- **Cognitive difficulties** caused by AEDs limit effective social and occupational functioning.
- **Cognitive performance** may also be reduced by subclinical seizures. For patients without childhood onset seizures, intelligence is usually otherwise normal.
- **Driving** in many states patients must be seizure free for one year before they may obtain a driver’s licence.
- **Alcohol consumption** moderate use may be tolerated. Heavy use can exacerbate seizures.
- **Return to work** should be recommended on an individual basis, according to the patient’s abilities and needs.
- **Death** from epilepsy is rare. When it does occur, it is usually due to status epilepticus or seizures that occur while driving, swimming, bathing, at great heights, or near dangerous objects.

**Treatment**

**Goals**

- Total control of seizures is possible in <75% of patients. For the remainder, a balance between partial control and adverse medication effects may need to be struck unless referral to a specialized epilepsy center is made.

**Drug choice**

- Seizure type and patient’s tolerance for side effects determine drug choice (see Table 34.1).
- There is no solid evidence that any one antiepileptic drug (AED) is more effective than another in controlling partial seizures, the most common kind.
- Sedative antiepileptic drugs (barbiturates and benzodiazepines) are less desirable than others because of negative effects on cognition and memory.

**Drug dosing**

- Start drugs slowly and increase the dose gradually to reduce toxicity.
- Drug half-life determines dosing interval. Agents with a half-life of 24 hours should be given once daily.
- Frequent administration (after meals and at bedtime) reduces peaks and troughs, and maximizes total daily intake with less toxicity. However, frequent administration may decrease compliance.

**Indications for measuring AED levels**

- To monitor compliance. For patients stabilized on medications, non-compliance is the most common cause of recurrence. Levels should be measured at least annually.
- When breakthrough seizures occur.
- When the patient has signs or symptoms of drug toxicity.

Refer patients to the Epilepsy Foundation (1-800-EFA-1000), an excellent resource for group support, information, and counseling.

Epileptic patients are protected by the Americans with Disabilities Act.

**First aid for a generalized tonic clonic seizure**

**Family education**

- All family members should know the basic principles of assisting a patient during a grand mal seizure.

**During the seizure**

- The patient should be prone.
- Remove eyeglasses.
- Loosen the necktie or any tight clothing around the neck.
- Do not restrain the patient.
- Do not place anything in the patient’s mouth.

**After the seizure**

- Turn the patient to the side to avoid aspiration of saliva.
- Observe until the patient is fully awake.

**Reference Ranges for Anti-Epilepsy Drugs (mg/dl)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapeutic</th>
<th>Toxic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbital</td>
<td>10–40</td>
<td>&gt; 60</td>
</tr>
<tr>
<td>Valproate</td>
<td>50–100</td>
<td>&gt; 150</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>6–12</td>
<td>&gt; 14</td>
</tr>
</tbody>
</table>


**Table 34.1 Which antiepileptic drug for which seizure type?**

<table>
<thead>
<tr>
<th>Seizure type</th>
<th>First choice agents</th>
<th>Second choice agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple</td>
<td>Carbamazepine</td>
<td>Gabapentin</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td></td>
<td>Valproate</td>
<td></td>
</tr>
<tr>
<td>Complex</td>
<td>Carbamazepine</td>
<td>Gabapentin</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td></td>
<td>Valproate</td>
<td>Levetiracetam</td>
</tr>
<tr>
<td></td>
<td>Oxcarbazepine</td>
<td>Zonisamide</td>
</tr>
<tr>
<td>Generalized</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Typical absence</td>
<td>Ethosuxamide</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td></td>
<td>Valproate</td>
<td></td>
</tr>
<tr>
<td>Atypical absence</td>
<td>Valproate</td>
<td>Ethosuxamide</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>Tonic clonic and other generalized</td>
<td>Valproate</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>seizures</td>
<td>Carbamazepine</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td></td>
<td>Oxcarbazepine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
<td></td>
</tr>
<tr>
<td>Myoclonic seizures</td>
<td>Valproate</td>
<td>Clonazepam</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acetazolamide</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zonisamide</td>
</tr>
</tbody>
</table>

* (Drugs are listed in order of preferred use.)

- When beginning another drug that may affect AED drug levels.
- Measure AED levels before and after starting the new agent.

**Interpretation of serum AED levels**

- Dose is determined by clinical response, not drug serum level. If the patient is seizure free, raising the dose will not reduce risk of future seizures but will increase toxicity, even if the level is subtherapeutic.\(^{11}\)
- The usually effective plasma concentration may be exceeded to achieve seizure control if the patient is not experiencing significant drug toxicity.
- A steady state should be reached before blood levels are drawn, unless the patient is experiencing significant toxicity. Five half-lives are needed to reach a steady state.
- The morning trough level should be measured, since diurnal variations occur.

**Monotherapy versus combination therapy**

- Monotherapy is preferred.
- The dose of one drug should be increased until seizures are controlled or side effects occur.

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If the first drug fails, a second drug should be tried alone.
The dose of the second agent should be maximized before a combination of two drugs is used together.
Combination therapy results in total control of seizures in 10% of patients not controlled on monotherapy. An additional 40% experience a reduction in seizure frequency.\textsuperscript{12}

American Academy of Neurology AED cessation guidelines
Cessation of therapy should be considered if the following criteria are met:\textsuperscript{13}
- The patient has been seizure free for 2–5 years.
- The patient has a single type of partial or generalized seizure.
- The patient has a normal neurologic exam and a normal IQ.
- The patient’s EEG has normalized with therapy.

Outcomes of cessation of therapy\textsuperscript{14}
- At two years, 78% of patients assigned to continue AEDs are seizure free, compared to 59% of those who slowly withdraw therapy (ARR = 19%).\textsuperscript{12}
- See below for the RR of recurrence. A clinical prediction rule that may be completed with a calculator is found in Table 34.2.

<table>
<thead>
<tr>
<th>Calculation of raw score (“Z score”)</th>
<th>Calculation of risk of seizure recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient characteristics</strong></td>
<td><strong>Within one year of continued AED treatment</strong></td>
</tr>
<tr>
<td>- Baseline score for all patients</td>
<td>- Within two years of continued AED treatment</td>
</tr>
<tr>
<td>- Age 16 or older</td>
<td>- Within one year after starting slow withdrawal of drug therapy</td>
</tr>
<tr>
<td>- Taking more than one AED treatment</td>
<td>- Within two years after starting slow withdrawal of drug therapy</td>
</tr>
<tr>
<td>- Seizures after start of AED treatment</td>
<td>- History of primary or secondarily generalized tonic clonic seizures</td>
</tr>
<tr>
<td>- History of myoclonic seizures</td>
<td>- EEG result within previous year</td>
</tr>
<tr>
<td>- Number of years free from seizures (NYFS)</td>
<td>- Not available</td>
</tr>
<tr>
<td>Total sum of above score “Z score”</td>
<td>- Abnormal</td>
</tr>
<tr>
<td></td>
<td>+(200 ÷ NYFS)</td>
</tr>
</tbody>
</table>

Relative Risk of Seizure Recurrence after Cessation of Therapy

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>RR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of partial seizures</td>
<td>2.51 (1.00 to 6.30)</td>
</tr>
<tr>
<td>History of myoclonic seizures</td>
<td>1.85 (1.09 to 3.12)</td>
</tr>
<tr>
<td>History of tonic clonic seizures</td>
<td>3.40 (1.48 to 7.84)</td>
</tr>
<tr>
<td>Seizures after beginning AEDs</td>
<td>1.57 (1.10 to 2.24)</td>
</tr>
<tr>
<td>Taking &gt;1 AED</td>
<td>1.79 (1.34 to 2.39)</td>
</tr>
<tr>
<td>Seizure free for 3 to &lt;5 years</td>
<td>0.67 (0.48 to 0.93)</td>
</tr>
<tr>
<td>Seizure free for 5 to &lt;10 years</td>
<td>0.47 (0.32 to 0.69)</td>
</tr>
<tr>
<td>Seizure free for &gt;10 years</td>
<td>0.27 (0.15 to 0.48)</td>
</tr>
</tbody>
</table>

Indications for referral to a specialized epilepsy center

- Satisfactory control is not achieved in a primary care setting within three months or with the help of a neurologist within one year.
- Disabling symptoms, either from the seizures or aggressive therapy. Surgery or other therapy may be helpful.
- For tumor or epileptogenic lesion removal when EEG/CT/MRI show localization or when seizures or AED side effects are unacceptable.
  - Complex partial seizures remit in 65–85% of patients who undergo temporal lobe resection.
  - Extratemporal resections without demonstrated structural lesions are less successful.
  - Postoperative neurologic deficit, hemiparesis, homonymous hemianopia, and language or memory loss occur in <5%.
- For vagus nerve stimulation (VNS). This is indicated in patients with intractable partial seizures who have failed AEDs and are not candidates for surgery. VNS is a pacemaker-like device connected to a programmable generator. It stimulates the left vagus nerve in the neck and modestly reduces seizure frequency. In a randomized single blind study, 31% of treatment patients compared to 13% of sham VNS controls experienced at least 50% fewer seizures.
- Palliative corpus callosotomy may benefit patients with frequent drop attacks who are at risk of serious head trauma.

Special situations

Seizures, fertility, and pregnancy

- Fertility is lowered primarily in patients with mental retardation or cerebral palsy (OR compared to the general population = 22).
- There is an increased rate of oral contraceptive failure due to drug interaction with phenytoin, phenobarbital, primidone, and carbamazepine. Oral contraceptives are still superior to barrier contraceptives in this setting.
- During pregnancy there are no adverse fetal outcomes in over 90% of cases; however, 25–30% of women experience an increased incidence of seizures.
Treatment with some AEDs can reduce serum or erythrocyte folate levels, which increases risk of fetal neural tube defects. Since many pregnancies are unplanned, folic acid ≥ 0.4 mg qd should given to all women of reproductive age taking AEDs.

AED therapy should be optimized before conception and drug withdrawal should be completed by six months before pregnancy; frequent seizures expose the fetus to greater risk than AEDs.

If possible, monotherapy is preferable.

Breast feeding is not contraindicated in women taking AEDs; however, newborns should be monitored for sedation.

**Alcohol withdrawal seizures (AWS)**

- These usually occur after several years of alcohol dependence.
- They are usually generalized convulsive seizures, single or several in a short series, occurring especially during withdrawal.
- They usually begin 7–48 hours after cessation of drinking, with a peak incidence at 13–24 hours.
- The EEG may be abnormal due to the direct effects of alcohol, metabolic disturbances, or previous head trauma.
- CT scan is indicated in this setting, as it alters management in ~4% of these patients. Clinically significant lesions include chronic subdural hematomas, subdural hygromas, neurocysticercosis, arteriovenous malformations, and arterial aneurysms.

- If no underlying structural lesion is detected and the patient does not have an epileptic disorder, antiepileptic drugs are not indicated. They may actually worsen alcohol withdrawal seizures.
- The treatment of choice is aggressive management of alcohol withdrawal for primary prevention of seizures. Treatment with intravenous benzodiazepines reduces the risk of recurrent seizures. The ARR for recurrence within six hours is 21%.

**Alcohol Withdrawal Seizure Recurrence Rate: Lorazepam v Placebo**

<table>
<thead>
<tr>
<th>Result</th>
<th>Rate (as % of all patients with AWS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>43</td>
</tr>
<tr>
<td>Generalized enlarged CSF spaces</td>
<td>38</td>
</tr>
<tr>
<td>Clinically significant intracranial lesion</td>
<td>6</td>
</tr>
<tr>
<td>Anterior cerebellar atrophy</td>
<td>5</td>
</tr>
<tr>
<td>Focal brain lesion due to old injury</td>
<td>5</td>
</tr>
<tr>
<td>Other: clinically insignificant</td>
<td>3</td>
</tr>
</tbody>
</table>

**Recurrence in <6h**

| Lorazepam | 3% | 1.5% |
| Placebo   | 24%| 14%  |


There is a higher rate of neural tube defects associated with valproic acid and carbamazepine. There is a higher risk of other malformations, including cardiac defects and cleft palate, with other AEDs. These patients should be considered for α fetoprotein testing and ultrasound at 16 and 18 weeks and possible amniocentesis.


**CT Results in Patients with Alcohol Withdrawal Seizures (AWS)**

<table>
<thead>
<tr>
<th>Result</th>
<th>Rate (as % of all patients with AWS)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>5</td>
</tr>
<tr>
<td>Other: clinically insignificant</td>
<td>3</td>
</tr>
</tbody>
</table>

23 D’Onofrio G, Rathke NK, Ulrich AS et al. Lorazepam for the prevention of recurrent seizures related to alcohol. N Engl J Med 1999;340:915–19. Double blind trial of 186 patients randomized to lorazepam 2mg IV x 1 dose v injection of 4 cc of normal saline IV. Patients with moderate or severe alcohol withdrawal were excluded from the trial.
<table>
<thead>
<tr>
<th>Drug</th>
<th>$T_1^1$ (h)</th>
<th>Dosage forms (mg)</th>
<th>Usual dosage (mg)</th>
<th>Adverse effects/comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetazolamide (Diamox)</td>
<td>12 ± 2</td>
<td>125/250/500</td>
<td>2–15 mg/kg bid</td>
<td>Lethargy, appetite suppression, paresthesia, kidney stones, metabolic acidosis. Renally excreted. Avoid in patients with sulfa allergy. Start at 250 mg/d.</td>
</tr>
<tr>
<td>Carbamazepine (Tegretol)</td>
<td>15 ± 5</td>
<td>100/200</td>
<td>100 tid–400 qid</td>
<td>Dizziness, diplopia, leukopenia. Start at 100 mg tid and increase at weekly intervals by up to 200 mg/d.</td>
</tr>
<tr>
<td>Clonazepam (Klonopin)</td>
<td>23 ± 5</td>
<td>0.5/1/2</td>
<td>0.5–5 tid</td>
<td>Sedation, confusion, ataxia, depression. Schedule IV drug. Start at 0.5 mg tid and increase dose by 0.5 mg/d to 1.0 mg/d every three days until adequate control or side effects occur.</td>
</tr>
<tr>
<td>Divalproex (Depakote)</td>
<td>14 ± 3</td>
<td>125/250/500</td>
<td>15–60 mg/kg/d</td>
<td>Anorexia, nausea, vomiting, somnolence, dizziness. Start at 15 mg/kg/d. Increase by 5–10 mg/kg/d every week until effective or side effects occur.</td>
</tr>
<tr>
<td>Ethosuxamid (Zarontin)</td>
<td>45 ± 8</td>
<td>250</td>
<td>500–2000 qd</td>
<td>Nausea, vomiting, GI side effects. Increase dose by 250 mg/kg/d every 4–7 days until effective or side effects occur.</td>
</tr>
<tr>
<td>Felbamate (Felbatol)</td>
<td>21 ± 2</td>
<td>400/600</td>
<td>400–1200 tid</td>
<td>Aplastic anemia, hepatitis, nausea, vomiting, headache, insomnia. 90% excreted by kidneys. Requires frequent monitoring of CBC and LFTs. The FDA originally recommended that patients be taken off this drug. It is now available for selected patients.</td>
</tr>
<tr>
<td>Gabapentin (Neurontin)</td>
<td>6 ± 1</td>
<td>100/300/400</td>
<td>300–1200 tid</td>
<td>Somnolence, dizziness, ataxia. Does not have any significant drug interactions with other AEDs. Dose adjustment necessary for renal failure. Dosage of 1800–2400 mg/d must be achieved to evaluate efficacy.</td>
</tr>
<tr>
<td>Lamotrigine (Lamictal)</td>
<td>20 ± 5</td>
<td>25/100/150/200</td>
<td>25–300 bid</td>
<td>Dizziness, ataxia, rash, weight gain, somnolence. Few drug interactions with other AEDs. Titrate from 25 mg/d to 50 mg/d on week 3 and to 100 mg/d on week 5. On week 7 begin titrating up 100 mg/d every week to effective dose. In patients also taking valproic acid, begin</td>
</tr>
</tbody>
</table>
### Table 34.3  Continued.

<table>
<thead>
<tr>
<th>Drug</th>
<th>$T_1^1$ (h)</th>
<th>Dosage forms (mg)</th>
<th>Usual dosage (mg)</th>
<th>Adverse effects/comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levetiracetam</td>
<td>7 ± 1</td>
<td>250/500/750</td>
<td>500–1500 bid</td>
<td>Somnolence, asthenia, psychiatric symptoms. Start at 1000 mg/d and increase by 1000 mg/d every two weeks until effective or side effects occur.</td>
</tr>
<tr>
<td>(Keppra)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>9 ± 1</td>
<td>150/300/600</td>
<td>600–1200 bid</td>
<td>Somnolence, dizziness, diplopia, ataxia. Start at 600 bid and increase by 600 mg/d at weekly intervals until effective or side effects occur.</td>
</tr>
<tr>
<td>(Trileptal)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>99 ± 18</td>
<td>15/30/60/100</td>
<td>90–300 qd</td>
<td>Sedation, rash, dizziness, ataxia. Schedule IV drug.</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>15 ± 9</td>
<td>30/100</td>
<td>100–300 bid</td>
<td>Nystagmus, ataxia, rash, hypertrichosis, macrocytosis, gingival hyperplasia, osteomalacia, lymphadenopathy</td>
</tr>
<tr>
<td>(Dilantin)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primidone</td>
<td>15 ± 4</td>
<td>50/250 (scored)</td>
<td>50–500 tid</td>
<td>Sedation, dizziness, nausea, ataxia, nystagmus. Begin at 125 mg qHs. On day 4 increase to 125 mg bid. On day 7 increase to 125 mg tid as tolerated.</td>
</tr>
<tr>
<td>(Mysoline)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>22 ± 2</td>
<td>25/100/200</td>
<td>200–500 bid</td>
<td>Somnolence, weight loss, nervousness. Excreted 70% by kidney. Start at 50 mg/d and increase dose by 25–50 mg/d every week until effective or side effects occur.</td>
</tr>
<tr>
<td>(Topamax)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproic acid</td>
<td>14 ± 3</td>
<td>250</td>
<td>7.5–30 mg/kg bid</td>
<td>Anorexia, nausea, vomiting, somnolence. Start at 10–15 mg/kg/d. Increase by 5–10 mg/kg/d every week until effective or side effects occur.</td>
</tr>
<tr>
<td>(Depakene)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zonisamide</td>
<td>59 ± 9</td>
<td>100</td>
<td>200–300 bid</td>
<td>Somnolence, dizziness, ataxia, headache, renal calculi. Start at 100–200 mg day and increase by 100 mg/d every two weeks until effective or side effects occur. Avoid in patients with sulfa allergy.</td>
</tr>
<tr>
<td>(Zonegran)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Drug interactions between AEDs and between AEDs and other medications are common and very complex. See manufacturers’ recommendations.
35 Sexually transmitted diseases
Esther Butler

Epidemiology

- Cases reported to the CDC in 1999:
  - Chlamydia: 659,441 (8.5% increase since 1998, steady increase since 1984)
  - Gonorrhea: 360,076 (10% increase since 1997, after a 72% decrease from 1977–97)
  - Syphilis (1°, 2°): 6,657 (88% decrease from 1990–99)
  - Chancroid: 143 (steady decline since 1988)
  - Herpes: 22% of population seropositive (NHANES-III).

General principles of management

- Avoidance of sexual intercourse with infected partners is the most effective way to prevent sexually transmitted diseases (STDs). Use of condoms is felt to be helpful.
- Patients should be advised about safe sex practices. Patients should be counseled to test themselves and partners for HIV and other STDs before initiating sexual intercourse.
- Characteristics that increase risk for STDs include:
  - multiple sex partners
  - unprotected sex
  - previous STD
  - commercial sex work
  - adolescent age.
- Patients with one STD frequently have another and should be screened appropriately for:
  - syphilis (RPR)
  - gonorrhea (culture or DNA probe)
  - chlamydia (culture or DNA probe)
  - HIV (ELISA antibody).
- Presence of STDs may increase HIV infectivity. Treatment of STDs may be helpful in controlling HIV.

Genital herpes

Epidemiology

- Nearly 22% of the adult population have HSV seropositivity but less than 10% report a history of genital herpes infection. Those who do not have a history of clinical herpes are probably a reservoir for spreading infection.
- 75–85% of genital herpes infections are caused by HSV-2; the remainder are caused by HSV-1. Genital herpes infections caused by HSV-2 and HSV-1 are clinically indistinct. HSV-1 is the primary cause of oral infections.

Guideline recommendations have been adapted from:

3. Cohen MS, Hoffman IF, Royce RA et al. Reduction of concentration of HIV-1 in semen after treatment of urethritis: implications for prevention of sexual transmission of HIV-1. 86 HIV positive men with urethritis were found to have eight-fold higher HIV RNA in semen than controls without urethritis but similar CD4 counts. Patients were treated for gonorrhea, syphilis, or chlamydia as needed. After two weeks HIV RNA in their semen decreased from 120,000 to 40,000 copies/ml, but serum RNA levels remained constant.
5. Wald A, Zeh J, Selke S et al. Reactivation of genital herpes simplex virus type 2 infection in asymptomatic seropositive persons. N Engl J Med 2000;342:844–50. 72% of subjects with HSV seropositivity but no clinical history of genital herpes were found to have HSV in genital cultures.
• HSV antibody tests cannot accurately distinguish between HSV-1 and HSV-2. The CDC does not currently recommend their use.
• Many HSV-2 infected patients have mild unrecognized infections and can transmit the infection unknowingly.
• About 90% of patients with first episode HSV-2 infection will have a recurrence within one year (median: four recurrences). 6
• Transmission occurs via contact with someone who is shedding the virus through skin lesions, mucosal surfaces, or other secretions. HSV can be transmitted during periods of asymptomatic shedding. Such shedding can occur at any point in a patient’s lifetime, although it is heaviest during the first six months after primary infection.

Diagnosis

Primary outbreak
• During the initial outbreak, patients usually have multiple, painful, grouped vesicles on an erythematous base. Vesicles may rupture to produce ulcerations of the vulva, cervix, vagina, or penis.
• Many patients have systemic symptoms, including fever, malaise, and headache. Lesions may last three or more weeks before healing.
• The rectal and perianal area may also be involved. Bilateral inguinal adenopathy is common.

Secondary outbreaks
• In secondary (recurrent) outbreaks, there is usually a prodrome of tingling or pain 30 minutes to 48 hours prior to the appearance of vesicles.
• Secondary outbreaks are usually less painful, more localized, and of shorter duration (3–7 days).

Confirmation of diagnosis
• The diagnosis can be made clinically if typical painful, multiple lesions are present.
• Lab confirmation is by viral inclusion bodies and multinucleated giant cells seen on Tzanck smear (Giemsa staining of scrapings from the base of a lesion) or by culture of vesicle fluid.

Treatment
• Patients should avoid sexual contact during outbreaks and should use condoms at all other times.
• Recommended oral antiviral regimens include acyclovir, famciclovir and valacyclovir. They appear to be equally efficacious, but the latter two have more convenient dosing schedules.
• Randomized trials have shown that antiviral therapy, when instituted during the prodrome or within one day of onset of lesions, provides partial control of symptoms for both primary7 and recurrent8 episodes. All three antiviral agents


Tzanck smear is only about 50% sensitive; a negative smear does not rule out herpes if the clinical picture is consistent with the diagnosis.


8 Sacks SL, Aoki FY, Diaz-Mitoma F et al. Patient-initiated, twice daily oral famciclovir for early recurrent genital herpes. JAMA 1996;276:44–9. 497 patients were randomized to self administer famciclovir or placebo at the first sign of recurrence. Median time to healing was 3.8–4.1 days for three different doses of famciclovir v 4.8 days for placebo.
appear to be equally effective and shorten episodes by about one day compared with placebo.7,9

- Antiviral therapy does not affect the clinical course once the drugs are discontinued.
- Topical antivirals are substantially less effective than the oral preparation and are not recommended for genital herpes.10
- Extra prescriptions for antiviral therapy should be given to patients diagnosed with genital HSV-2 who are to be treated for recurrence. Patients should be instructed to begin medication immediately at the first sign of lesions or prodrome.
- Daily suppressive therapy should be considered for patients with frequent recurrences. It reduces the frequency of HSV recurrences11 and minimizes, but does not necessarily eliminate, asymptomatic shedding.12 Suppressive therapy should be discontinued after one year to re-evaluate the patient’s rate of recurrence.
- Symptomatic sex partners of patients should be treated. Asymptomatic partners should be examined and questioned about current and past genital lesions. They should also be counseled about risk of transmission of HSV even during asymptomatic periods and encouraged to seek medical attention promptly if genital lesions appear.

### Antibiotic Therapy for Genital Herpes

**Primary infection** (7–10 days treatment)
- Acyclovir (Zovirax) 200 mg PO 5 ×/d or 400 mg tid
- Famciclovir (Famvir) 250 mg PO tid
- Valacyclovir (Valtrex) 1 gram PO bid

**Episodic recurrent infection** (5 days treatment)
- Acyclovir 200 mg PO 5 ×/d or 400 mg tid or 800 mg bid
- Famciclovir 125 mg PO bid
- Valacyclovir 500 mg PO bid

**Daily suppressive therapy**
- Acyclovir 400 mg PO bid
- Famciclovir 250 mg PO bid
- Valacyclovir 500 mg PO qd or 1 g qd

### Syphilis (reponema pallidum)

**Diagnosis**

*History and physical exam*

- **Primary**: painless ulcer or chancre at site of infection usually 3–4 weeks after exposure.
- **Secondary**: rash, mucocutaneous lesions, adenopathy, and flu-like symptoms occurring 6–8 weeks after primary infection.
- **Latent syphilis**: patients are seroactive but asymptomatic
  - Early latent <1 year duration
  - Late latent >1 year duration
  - Latent syphilis of unknown duration should be managed as late latent syphilis.
SEXUALLY TRANSMITTED DISEASES

- Tertiary: neurologic, ophthalmic, auditory, cardiac, and gummatous lesions.

Laboratory tests
- The gold standard is dark field examination and direct fluorescent antibody test of lesion exudate or tissue.
- Diagnosis is made with a non-treponemal (reagin) test (VDRL or RPR). Confirmation by a treponemal test (FTA-ABS or MHA-TP) is required because of the high false positive rate of the non-treponemal tests.
- False positive non-treponemal tests usually have a titer < 1:16.
- VDRL/RPR usually correlates with disease activity; a fourfold change in titer is considered a clinically significant difference between two test results. Patients should be re-evaluated serologically six and 12 months after treatment.
- VDRL/RPR may become negative after treatment; however, many patients remain positive. If titers increase fourfold within 1–2 years or if an initially high titer (> 1:32) fails to decrease, consider treatment failure or reinfection. Patients should be retreated and tested for HIV. Unless reinfection is certain, a lumbar puncture should be performed.
- The same testing method (VDRL or RPR) should be used to follow disease activity.
- After treatment, titers progressively decline. Many patients become seronegative within two years. This occurs more commonly after treatment for primary than after secondary or latent syphilis.
- Treponemal tests (MHA-TP) usually remain positive for life regardless of treatment or disease activity.
- Pregnant women and high risk persons should be screened with VDRL.
- All patients with syphilis should be tested for HIV.

Treatment
- Penicillin G is the treatment of choice for all stages. The specific preparation, dose, and duration depend on the stage of syphilis. Little research has been done recently on syphilis treatment.
- Parenteral penicillin G is the only therapy with documented effectiveness in the setting of neurosyphilis and syphilis during pregnancy. Therefore, such patients with penicillin allergy should be desensitized and treated with penicillin if possible.
- For severe penicillin allergy or cases in which desensitization is not possible, tetracycline, erythromycin, and cephalosporins are alternatives.
- HIV positive patients are at an increased risk for neurologic complications and treatment failure. HIV positive patients with any stage of syphilis should have a lumbar puncture for cerebrospinal fluid VDRL before treatment is begun.
- The Jarisch-Herxheimer reaction is an acute febrile reaction that may occur within 24 hours after initiation of therapy.
Sex partners should be examined and evaluated serologically and treated appropriately. Seronegative sex partners who have been exposed to persons with primary, secondary, or early latent syphilis within the preceding 90 days should be treated presumptively.

VDRL titers should be repeated at three, six, and 12 months to document response. Consider treatment failure if symptoms persist or titers fail to decrease fourfold within three months after therapy.

**Antibiotic Therapy for Syphilis**

- **Primary, secondary and early latent**: benzathine penicillin G 2.4 million units IM × 1
- **Late latent or unknown duration**: benzathine penicillin G 2.4 million units IM q week × 3 doses
- **If penicillin allergic (and unable to desensitize)**: Doxycycline 100 mg PO bid × 14 days
  Tetracycline 500 mg PO qid × 14 days

**Gonorrhea (Neisseria gonorrhoeae)**

**Epidemiology and diagnosis**

**History**

- In men, gonorrhea usually presents with dysuria and urethral discharge.
- The most common symptoms in women are dysuria, frequency, and vaginal discharge related to cervicitis; however, women are frequently asymptomatic until complications have occurred.
- In 2% of cases, gonorrhea infection is disseminated. Patients may have fever, septicemia, dermatitis, arthritis, endocarditis, or meningitis.
- Complications of untreated infection include Bartholin’s gland abscess, pelvic inflammatory disease, spontaneous abortion, and premature rupture of membranes during pregnancy.
- Because women are frequently asymptomatic and because gonorrhea is easily cured when detected early, routine screening is recommended for all high risk women and is the primary method of control.

**Physical exam and laboratory tests**

- In women, physical exam is frequently unremarkable; men may have evidence of urethral discharge on their underwear.
- Diagnosis is made by culture of the urethra in men and the cervical os in women, but the DNA probe test is nearly as accurate.
- Pharyngeal infection may produce exudative tonsillitis but is frequently asymptomatic.
- Gram stain may also be used, but sensitivity is only 50–70%. N. gonorrhoeae are Gram negative intracellular diplococci.

The Tuskegee episode permanently affected syphilis research and medical research in general. In 1932 the US Public Health Service offered “free treatment” to 399 poor black men in Tuskegee, Alabama. The subjects were given only aspirin and followed prospectively to determine the natural history of untreated syphilis. The experiment was not halted in 1947 when penicillin was universally recognized as the standard of care for syphilis and the Nuremberg trials of Nazi medical atrocities codified the concept of informed consent. In fact, the Tuskegee protocol continued until 1972, when the story was uncovered by a journalist. Wolinsky H. Steps still being taken to undo damage of “America's Nuremberg”. Ann Intern Med 1997;127:143–4.

In October 1999, the FDA and CDC announced a shortage of intravenous penicillin G due to decreased production by a major manufacturer. The lack of profitability from a generic drug may be another reason why little research has been done in the area of syphilis treatment.

N. gonorrhoeae is grown on Thayer-Martin media (chocolate agar containing antibiotics). If an incubator is not available, culture plates should be transported to the lab as soon as possible.

| Young H, Anderson J, Moyes A, McMillan A. Non-cultural detection of rectal and pharyngeal gonorrhoea by the Gen-Probe[R] PACE[R] 2 Assay. Genitourin Med 1997;73:59–62. Sensitivity and specificity of Gen-Probe were 94% and 100% for rectal specimens, 86% and 100% for pharyngeal specimens compared with culture as a gold standard in gay men attending a urology clinic. | 13 |
Treatment

- Gonorrhea can be treated with a single dose of antibiotics, typically a cephalosporin.14
- Forty to fifty percent of persons with gonorrhea are also coinfected with C. trachomatis; all patients should be empirically treated for chlamydia. Azithromycin can treat both illnesses.15
- Patients do not need to be retested after treatment unless symptoms persist.
- All sex partners within the previous 60 days should be treated. The most recent sexual contact of any duration should be evaluated and treated. Patients should avoid all sexual intercourse until therapy is complete and any symptoms have resolved.

Gonorrhea Treatment

- Ceftriaxone 125 mg IM × 1
- Cefixime 400 mg PO × 1
- Ciprofloxacin 500 mg PO × 1
- Ofloxacin 400 mg PO × 1
- Plus an antibiotic to cover C. trachomatis (possibly azithromycin 2 g to cover both)

Chlamydia (Chlamydia trachomatis)

Diagnosis

- Chlamydia is the most common bacterial STD in the US and the prevalence has been increasing steadily.
- Adolescents and young adults have the highest rates of chlamydia.16
- Although the infection is frequently asymptomatic, it can cause non-gonococcal urethritis and acute epididymitis in men and mucopurulent cervicitis and pelvic inflammatory disease (PID) in women.
- Complications of untreated chlamydia include recurrent PID, ectopic pregnancy, and infertility. There is some evidence that treatment of chlamydia can prevent PID.17
- The antigen is detected by ELISA of secretions or staining of smears by direct immunofluorescence.18 DNA probe or PCR are also used to test for chlamydia. A ligase chain reaction test performed on random urine samples may allow diagnosis without a pelvic exam or painful urethral swab.19
- Women at high risk should undergo chlamydia screening during the gynecologic exam.
- Chlamydia trachomatis also causes lymphogranuloma venereum (tender unilateral inguinal adenopathy). There were 235 cases reported to the CDC in 1994.

Treatment

- Chlamydia is usually treated with a macrolide antibiotic. Single dose treatment is as efficacious as standard seven-day...
treatment and may be more cost effective, especially if compliance is in doubt.  
- There is a high rate of coinfection with Neisseria gonorrhoeae; patients should be empirically treated for both infections.
- Patients do not need to be retested after completing therapy unless symptoms persist.
- All sex partners within the previous 60 days should be evaluated and treated. The most recent sexual contact, no matter how distant, should be evaluated and treated.
- Patient and sex partner should abstain from sexual intercourse until after treatment is complete. If single dose therapy is used, patients should abstain for seven days after the single dose.

Chlamydia Treatment
- Doxycycline 100 mg PO bid × 7 days or
- Azithromycin 1 g PO × 1
  — Plus an antibiotic to cover N. gonorrhoeae

Chancroid (Haemophilus ducreyi)
Epidemiology and diagnosis
- Chancroid is much less common than the other STDs discussed.
- As many as 10% of patients may be coinfected with syphilis.
- Patients present with a combination of a painful ulcer with tender inguinal adenopathy. Suppurative inguinal adenopathy is almost pathognomonic.
- Presumptive diagnosis can be made if:
  — there are painful genital ulcers present
  — there is no evidence of syphilis on dark field exam or VDRL at least seven days after onset of the ulcers
  — the presentation is not typical of genital herpes and the HSV tests are negative.

Treatment
- Chancroid is usually treated with macrolides. Many experts recommend treatment for both syphilis and chancroid if the diagnosis is unclear.
- If initial tests for HIV and syphilis are negative, patients with chancroid should be tested three months later.

Chancroid Treatment
- Azithromycin 1 g PO × 1
- Erythromycin 500 mg PO qid × 7 d
- Ceftriaxone 250 mg IM × 1

Genital warts
- As many as 1% of sexually active adults may have genital warts (condylomata acuminata).  

20 Stamm WE, Hicks CB, Martin DH et al. Azithromycin for empirical treatment of the nongonococcal urethritis syndrome in men. A randomized double-blind study. JAMA 1995;274:545–9. 452 men in 11 sexually transmitted disease clinics were randomized to one dose of 1 g azithromycin v doxycycline, 100 mg twice daily for seven days. Clinical cures at two and five weeks were 90% v 89% and 89% v 85%, respectively. Adverse events were comparable and mild.


The chancre of primary syphilis is painless; the chancre of chancroid hurts.

The gold standard lab test for H. ducreyi is not commercially available.
• The morbidity from genital warts is primarily cosmetic and psychosocial; the warts usually cause no symptoms.
• The HPV types linked with cervical cancer (mainly 16, 18) are different from the types linked to genital warts (mainly 6, 11).
• Ten to thirty percent of lesions may resolve spontaneously within three months.
• The goal of treatment is cosmetic resolution, not HPV eradication, therefore patient preference and side effect profile are extremely important.
• Treatment of genital warts can be difficult and long term recurrence rates are high; however, there is some short term success with self administered topical imiquimod\textsuperscript{23} and podofilox.\textsuperscript{24}
• Other treatments for which there are some efficacy data require office visits:
  —topical podophyllotoxin resin
  —cryotherapy
  —intralesional interferon.
• There are few good quality data for the efficacy of topical or systemic interferon and bi- or trichloroacetic acid.
• It is not known how infectious subclinical HPV infection is or whether removal of warts reduces sexual transmission. In the absence of such data, sex partners probably do not need to be examined. Condoms may be recommended.

\begin{table}[h]
\centering
\caption{Agents for sexually transmitted diseases (CDC recommendation\textsuperscript{1}).}
\begin{tabular}{|l|l|}
\hline
\textbf{Genital herpes} & \\
\hline
Primary infection (7–10 days treatment) & \\
\quad Acyclovir (Zovirax) & 200 mg PO 5 × d or 400 mg PO tid \\
\quad Famciclovir (Famvir) & 250 mg PO 3 × d \\
\quad Valacyclovir (Valtrex) & 1 gram PO 2 × d \\
Episodic recurrent infection (5 days treatment) & \\
\quad Acyclovir & 200 mg PO 5 × d or 400 mg PO tid \\
\quad Famciclovir & 125 mg PO bid \\
\quad Valacyclovir & 500 mg PO bid \\
Daily suppressive therapy & \\
\quad Acyclovir & 400 mg PO bid \\
\quad Famciclovir & 250 mg PO bid \\
\quad Valacyclovir & 500 mg PO qd or 1 g PO qd (All antiherpetic drugs require decreased dosing in renal insufficiency) \\
\hline
\textbf{Syphilis} & \\
Primary, secondary and early latent & \\
\quad Benzathine penicillin G & 2.4 million units IM × 1 \\
\hline
\end{tabular}
\end{table}

\textsuperscript{23} Edwards L, Ferenczy A, Eron L et al. Self-administered topical 3% imiquimod cream for external anogenital warts. \textit{Arch Dermatol} 1998;134:25–30. 311 patients were randomized to self administered 5% or 1% imiquimod cream or placebo. At 16 weeks, 50% of patients using 5% cream had eradication of warts v 21% using the 1% cream and 11% using placebo.

\textsuperscript{24} Tyring S, Edwards L, Cherry LK et al. Safety and efficacy of 0.5% podofilox gel in the treatment of anogenital warts. \textit{Arch Dermatol} 1998;134:33–8. 62/167 (37%) of patients treated with self administered 0.5% podofilox gel had complete clearing of the treated areas compared with 2/66 (2.3%) of patients treated with placebo after four weeks.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late latent or unknown duration</td>
<td>2.4 million units IM q week × 3 doses</td>
</tr>
<tr>
<td>Benzathine penicillin G</td>
<td></td>
</tr>
<tr>
<td>If penicillin allergic (and unable to desensitize)</td>
<td></td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100 mg PO bid × 14 days (Avoid sunlight)</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>500 mg PO qid × 14 days</td>
</tr>
<tr>
<td><strong>Gonorrhea</strong></td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone (Rocephin)</td>
<td>125 mg IM × 1</td>
</tr>
<tr>
<td>Cefixime (Suprax)</td>
<td>400 mg PO × 1 (Reduce dose with renal impairment)</td>
</tr>
<tr>
<td>Ciprofloxacin (Cipro)</td>
<td>500 mg PO × 1 (Renal and hepatic dosing, avoid sunlight)</td>
</tr>
<tr>
<td>Ofloxacin (Floxin)</td>
<td>400 mg PO × 1</td>
</tr>
<tr>
<td><em>plus</em> an antibiotic to cover <em>C. trachomatis</em> (possibly azithromycin 2 g to cover both)</td>
<td></td>
</tr>
<tr>
<td><strong>Chlamydia</strong></td>
<td></td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100 mg PO bid × 7 days or</td>
</tr>
<tr>
<td>Azithromycin (Zithromax)</td>
<td>1 g PO × 1</td>
</tr>
<tr>
<td><em>plus</em> an antibiotic to cover <em>N. gonorrhoeae</em></td>
<td></td>
</tr>
<tr>
<td><strong>Chancroid</strong></td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>1 g PO × 1</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>250 mg IM × 1</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>500 mg PO qid × 7 d</td>
</tr>
<tr>
<td><strong>Genital warts</strong></td>
<td></td>
</tr>
<tr>
<td>Podofilox 5% gel or solution (Condylox)</td>
<td>Apply to warts bid × 3 days then discontinue for 4 days, repeat cycle as needed</td>
</tr>
<tr>
<td>Imiquimod 5% cream (Aldara)</td>
<td>Rub a thin layer on warts qh 3 × /week (avoid mucous membranes), remove after 6–10 hours with soap and water, use for up 16 weeks (avoid mucous membranes, avoid sexual contact while on skin)</td>
</tr>
</tbody>
</table>
36 Smoking cessation
Danielle Ofri

Epidemiology
- Smoking contributes to 430,000 deaths each year in the United States – one out of five deaths.
- Smoking is the leading cause of preventable death.
- In the US, 24.7% of adults are current smokers.\(^1\)
- Cigars and smokeless tobacco are not safer than cigarettes.

Benefits of quitting
- Decreased coronary artery disease (CAD)
- Decreased stroke\(^2\)
- Decreased lung and oropharyngeal cancer\(^3\)
- Improved lung function
- Increased infant birth weight
- Increased life expectancy\(^4\)

Populations at high risk for smoking and its complications
- Pregnant women
- Mentally ill
- Alcoholics
- Patients with CAD, hypertension, diabetes, hyperlipidemia
- Adolescents

Treatment
Overview
- "The mere act of speaking": simple physician advice to quit smoking modestly improves cessation rates.\(^5\)
- Include “tobacco addiction” as an active issue in patients’ problem lists.
- Provide nicotine replacement therapy or pharmacologic assistance as indicated.
- Provide behavioral intervention, including referral to smoking cessation groups, if available.

Nicotine replacement therapy (NRT)
- Several meta-analyses have shown that NRT improves cessation rates (usually doubling the quit rates compared to placebo). NNTs range from 8 to 17. Gum and patch are the most studied forms.\(^6\)
- NRT is generally considered safe. Relative contraindications include severe angina, recent MI (within four weeks), and life threatening arrhythmias.
- Behavioral therapy is synergistic with NRT and should be recommended in addition. Studies of NRT with “minimal contact” (over the counter use) show six month quit rates of approximately 10% compared to 4% for placebo.\(^7\)
- Although rigorous studies about long term safety of NRT have not been done, subjects who have used nicotine gum...
for up to five years did not experience higher rates of cardiovascular or other disease.\textsuperscript{8}

- No studies have been done in pregnant women, but nicotine therapy is probably safer than smoking (no carbon monoxide exposure, lower nicotine levels).

**Transdermal nicotine ("the patch")**

- More than 16 RCTs and five meta-analyses show a consistent doubling of quit rates, from 10\% to 20\% on average.\textsuperscript{6}
- Provides continuous absorption and consistent blood levels.
- A major advantage of the patch is convenience and compliance. A disadvantage is lack of oral stimulation and immediate “buzz” (as with gum or inhaler).
- The patch should be applied to a relatively hairless area of skin between the neck and waist each morning, rotating sites.
- Local skin reactions are frequent, but generally mild.
- Patients must stop smoking before using the patch and not smoke while using the patch.
- There have been no direct comparisons between various brands.
- The patch may be used for 8–16 weeks.
- For <1/2 pack per day (ppd) or weight <100 pounds, replacement can start at a lower dose.
- The 24 hour per day patch is recommended for those who crave cigarettes first thing in the morning. The 16 hour per day patch is recommended when the patch causes insomnia or vivid dreams.
- Cost: about $5 per patch, $280 for eight weeks. Patients should be reminded that this compares favorably with the cost of cigarettes.

**Nicotine gum (nicotine polacrilex, nicotine resin complex)**

- Absorbed via oral mucosa, peak levels at 20 minutes.
- Advantages include oral stimulation and rapid buzz.
- Patients should chew the gum slowly until a peppery taste appears, then “park” the gum in the cheek until the taste disappears. Chew and park again.
- The “park” is extremely important (and frequently overlooked).
- Nicotine is absorbed via the oral mucosa (not the GI tract).
- Chew and park intermittently over 30 minutes.
- Do not eat or drink 15 minutes before or during gum use. Acid interferes with absorption; water is OK.
- Fixed dosing (every hour or 30 minutes) is more effective than prn.
- Available without a prescription in 2 and 4 mg strengths – 2 mg for <1/2 ppd or <100 pounds.
- Cost: about $60 for box of 108 pieces, $400–500 for eight weeks.

<table>
<thead>
<tr>
<th>Abstinence with NRT compared to control were:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gum</td>
</tr>
<tr>
<td>Patch</td>
</tr>
<tr>
<td>Nasal spray</td>
</tr>
<tr>
<td>Inhaled nicotine</td>
</tr>
<tr>
<td>Nicotine inhaler</td>
</tr>
</tbody>
</table>

\textsuperscript{7} Hughes JR, Hurt RD, Shiffman S. Recent advances in the pharmacotherapy of smoking. JAMA 1999;281:72–6.

\textsuperscript{8} Murray RP, Bailey WC, Daniels K et al. Safety of nicotine polacrilex gum used by 3094 participants in the Lung Health Study. Chest 1996;109:438–45.


Labels on OTC gum and patch warn users of asthma medications and inhalers to consult their MDs. This is not because there is an interaction between the gum or patch and these medications. The issue is that some of the non-nicotine components in cigarettes increase the metabolism of many medications; therefore, the cessation of smoking may increase the levels of these medicines. Refer to Miller LG. Cigarettes and drug therapy: pharmacokinetic and pharmacodynamic considerations. Clin Pharm 1990;9:125–35.

The following drugs should be monitored during smoking cessation and may require a dosage decrease:

- Insulin, \(\alpha\) and \(\beta\) blockers, heparin, imipramine, chlorpromazine, acetaminophen, caffeine

**Drugs that may require an increase upon cessation of smoking:**

- Adrenergic agonists

Package inserts warn against using the patch and gum together, but a small placebo controlled study showed slightly increased quit rates at three and six months (odds ratios 1.7–2, NNT = 8) with no additional adverse effects. The difference was no longer significant, however, at one year. Continued
Nicotine nasal spray
- Delivers nicotine more rapidly than gum, patch, or inhaler.
- The dose is 1–2 sprays in nostril per hour for three months.
- Initial adverse effects include rhinitis, sneezing, coughing, coryza, and irritation of nasal and pharyngeal mucosa.
- Most users experience these side effects, but there is significant tolerance after the first week.
- Cost: about $50 per bottle, $400 for eight weeks
- By prescription only

Nicotine inhaler
- Not a true inhaler because nicotine vapor is absorbed via the oral mucosa, not the lungs (no matter how deep the breath).
- Similar to gum in terms of pharmacodynamics and adverse effects.
- Most patients use 6–16 cartridges per day for up to 12 weeks.
- Bioavailability decreases below 50% at ambient temperature.
- Cost: about $55 per box of 42, $400–800 for eight weeks
- By prescription only

Non-nicotine pharmacotherapy
- Antidepressants work as smoking cessation aids in patients who are not depressed.
- Tobacco smoke releases norepinephrine, dopamine, and serotonin, and the antidepressants are felt to work by blocking the reuptake of these transmitters.

Bupropion
- The sustained release preparation of this atypical antidepressant has been approved by the FDA for smoking cessation.
- The best studied of all non-nicotine pharmacotherapies.
- The largest well designed study showed a one year quit rate of 23% versus 12% for placebo (ARR = 11%, NNT = 9).
- Treatment is initiated one week prior to the quit date: 150 mg PO qd x 3 days, then 150 mg PO bid x 8–12 weeks.
- Adverse effects include dry mouth, agitation, insomnia, and skin rash.
- Contraindications: history of seizure, head trauma, anorexia/bulimia, heavy alcohol use, recent MAO inhibitor use, post MI.
- Cost: about $200 for eight weeks

Nortriptyline
- A tricyclic antidepressant, not FDA approved for smoking cessation (and likely will never be because it is generic).
- There are only a few small controlled trials showing efficacy.
- Treatment is initiated two weeks prior to the quit date: 25 mg qd x 4 days, 50 mg qd x 4 days, then 75 mg qd x 12 weeks.


Abuse and dependence of NRT
This is difficult to quantify, as patients already have a dependence on nicotine. Nicotine nasal spray has the fastest onset of action and highest fluctuation of plasma levels and may cause more dependent behavior than the patch, which provides more stable plasma levels. Gum and inhalers are probably intermediate in this regard.


A study compared bupropion and the patch. At one year, bupropion alone had a statistically similar quit rate compared to bupropion plus the patch (about 30%). The patch alone, however, was no different from placebo (15%). This is different from most other studies of the patch. Jorenby DE, Leischow SJ, Nides MA et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. N Engl J Med 1999:340: 685–91.

Six-month quit rate was 14% for nortriptyline v 3% for placebo in a double blinded study. 78% of study nurses and 67% of patients were able to correctly guess treatment assignment. Prochaza AV, Weaver MJ, Keller RT, Fryer GE, Licari PA, Lofaso D. A randomized trial of nortriptyline for smoking cessation. Arch Intern Med 1998;158:2035–9.
Adverse effects and contraindications are similar to bupropion, but overall less sedating and anticholinergic than other tricyclics.

Cost is negligible.

Clonidine

- This centrally acting α agonist antihypertensive is not FDA approved for smoking cessation.
- Small studies of both oral and transdermal clonidine show reduction of withdrawal symptoms but not long term cessation.

Behavioral interventions

- Though nicotine produces pharmacological dependence, there is a large degree of learned behaviors tied in with smoking.
- Pharmacotherapy is rarely successful without some behavioral intervention.
- Behavioral interventions are more successful with increasing intensity of intervention and use of concomitant types of intervention (self help, brief physician counseling, support groups, one on one specialized counseling).
- Odds ratios for quitting with various types of behavioral intervention range from 1.2 to 2.4. Smoking Cessation Guideline Panel. Smoking Cessation. Clinical Practice Guideline No. 18. Agency for Health Care Policy and Research, Washington DC, 1996: 40–52. Patients should be given the most intense behavioral interventions available.

Practical strategies for smoking cessation in the primary care setting

- Identify every smoker.
- Keep “tobacco use” as an active problem.
- Encourage smoking cessation at every visit and list the health benefits of quitting.
- Choose a quit date (within 2–3 weeks).
- Arrange for counseling if available.
- Strongly consider NRT and/or bupropion
- Patient preparation:
  - Remove cigarettes and ashtrays.
  - Tell family, friends, and coworkers about the attempt to quit.
  - Enlist a spouse or friend to quit simultaneously.
  - Try not to smoke where most time is spent (house, car, office).
  - Anticipate difficult situations: on the telephone, at parties or restaurants, with food or alcohol.
- Prepare for anticipated weight gain with sensible measures such as a modest exercise program and having an adequate supply of low calorie foods.
- On the quit date, the patient must be 100% abstinent. It often helps to limit alcohol as well.
- MD follow up within one week is essential (may be by phone).

Smokers cite physician advice as an important motivator to quit, yet more than half were never told to quit by their doctors.

Smokers consider health benefits the most important reason to quit.

Weight gain

- Usually the biggest fear.
- Be honest: most people will gain some weight after quitting (usually less than 10 pounds).
- Remind the patient of the overwhelming health benefit of quitting smoking v the negligible health risk of adding a few pounds (though this generally provides little comfort).
- It’s important not to overwhelm the patient with trying to address two problems at once.

Resources

American Cancer Society
1-800-227-2345 (www.cancer.org)

American Lung Association
1-800-586-4872 (www.lungusa.org)

National Cancer Institute
1-800-4-CANCER (800-422-6237) (www.nci.nih.gov)

US Office on Smoking and Health
770-488-5705
• Continued follow up over the next several weeks.
• If the patient relapses, explain that several attempts are often needed. The majority of patients (>80%) do not succeed on the first attempt. Refer the patient who has relapsed to a specialized program.

Table 36.1  Aids to smoking cessation.

<table>
<thead>
<tr>
<th>Aids to Smoking Cessation</th>
<th>Dosage (as recommended by AHCPR)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine patches</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicoderm (OTC)</td>
<td>21 mg qd × 4 wks/ 14 mg qd × 2 wks/ 7 mg qd × 2 wks</td>
<td>Leave on for 24 hours</td>
</tr>
<tr>
<td>Habitrol (prescription)</td>
<td>21 mg qd × 4 wks/ 14 mg qd × 2 wks/ 7 mg qd × 2 wks</td>
<td>Leave on for 24 hours</td>
</tr>
<tr>
<td>Nicotrol (OTC)</td>
<td>15 mg qd × 4 wks/ 10 mg qd × 2 wks/ 5 mg qd × 2 wks</td>
<td>Remove at night</td>
</tr>
<tr>
<td>Prostep (prescription)</td>
<td>22 mg qd × 4 wks/ 11 mg × 4 wks</td>
<td>Leave on for 24 hours</td>
</tr>
<tr>
<td>Nicotine polacrilex chewing gum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicorette (2 mg)</td>
<td>Chew 1 piece q 1–2 hours</td>
<td></td>
</tr>
<tr>
<td>Nicorette DS (4 mg)</td>
<td>Maximum dose: 30 pieces of 2 mg or 20 pieces of 40 mg per day</td>
<td></td>
</tr>
<tr>
<td>Nicotine nasal spray</td>
<td>1–2 sprays in nostril per hour for 3 months</td>
<td></td>
</tr>
<tr>
<td>Non-nicotine therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion (Zyban)</td>
<td>150 mg PO qd × 3 days starting 1 week before quit date, then... 150 mg PO bid × 8–12 weeks</td>
<td></td>
</tr>
</tbody>
</table>
Thyroid disease may be present in more than 10% of the population, though many cases are subclinical.¹ In the outpatient setting, thyroid disease usually presents as hypothyroidism, hyperthyroidism, or a palpable abnormality on physical exam (nodule or goiter).

**Hypothyroidism**

**Epidemiology**

*Prevalence and risk factors*

- Hypothyroidism is most commonly seen in middle aged women, but the disease can occur at any age in both sexes.
- Having a first degree family member with hypothyroidism increases risk.
- There is also increased risk for idiopathic and chronic (Hashimoto’s) thyroiditis if the patient or a first degree family member has diabetes or an autoimmune disorder with circulating autoantibodies (pernicious anemia, lupus, rheumatoid arthritis, Sjögren’s syndrome, and chronic hepatitis).

**Etiology**

- Nearly all cases of hypothyroidism, with or without goiter, are caused by:
  - chronic autoimmune thyroiditis (Hashimoto’s disease), with or without goiter depending on the stage of the disease
  - iatrogenic following therapy for hyperthyroidism with ¹³¹I or surgery, usually without goiter.

**Other causes**

- Iatrogenic from other drugs
- Iodide deficiency
  - Usually in remote geographic areas
  - Typically presents with goiter
- Resolving subacute viral thyroiditis (also called granulomatous, giant cell, or de Quervain’s thyroiditis)
- Idiopathic atrophy
- Congenital developmental defect
- Pituitary: thyroid stimulating hormone (TSH) deficiency
- Hypothalamic: thyroid releasing hormone (TRH) deficiency

**Diagnosis**

**History**

- Hypothyroidism represents a general slowing down of metabolism. The presentation in adults can be highly variable, especially in elderly patients. The onset is often insidious and the symptoms can be vague and non-specific.
- The classic symptoms are easy fatiguability, cold intolerance, weight gain, muscle aches, dry skin, hair loss, hoarseness,

1. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med 2000;160:526–34. This population based survey of 25,682 participants found a 9.5% prevalence of elevated TSH levels and a 2.2% prevalence of decreased TSH levels.

**Medications that cause hypothyroidism**

- Antithyroid drugs
- Iodide
- Lithium
- Amiodarone
- Sulfonylureas

**Lithium**, like iodine, inhibits production of thyroid hormone as well as release of preformed hormone. In 100 bipolar patients treated with lithium, 4% and 21% developed some form of hypothyroidism after five and 10 years, respectively. Lithium may be continued with thyroxine supplementation or replaced with an alternative medication. Perrild H, Hegeds L, Baastup PC, Kayser L, Kastberg S. Thyroid function and ultrasonically determined thyroid size in patients receiving long-term lithium treatment. Am J Psychiatry 1990;147:1518–21.

**Amiodarone** is structurally similar to thyroid hormone and contains nearly 40% iodine. It affects thyroid physiology in all patients, but only 15% develop clinical hypothyroidism or hyperthyroidism. Even if amiodarone is discontinued, its effects may be long lasting (half-life up to four months) or permanent. Newman CM, Price A, Davies DW, Gray TA, Weetman AP. Amiodarone and the thyroid: a practical guide to the management of thyroid dysfunction induced by amiodarone therapy. Heart 1998;79:121–7.
constipation, depression, carpal tunnel syndrome, menorrhagia, and infertility. See Table 37.2 for the Billewicz index.

**Physical exam**
- These findings tend to be subtle and often do not appear early in the course of the disease: slow movements, bradycardia, and prolonged relaxation phase of the deep tendon reflexes.
- Thyroid enlargement may or may not be present, depending on the etiology of the hypothyroidism.²

**Laboratory tests**
- Serum thyroid-stimulating hormone (TSH or thyrotropin) is the most sensitive measure of thyroid function. An elevated TSH is indicative of primary hypothyroidism.

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**Table 37.1 Agents for Thyroid Disease.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage forms</th>
<th>Usual Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levothyroxine (Synthroid)</td>
<td>25/50/75/88/100</td>
<td>25–200 micrograms PO qd</td>
</tr>
<tr>
<td></td>
<td>112/125/200/300 micrograms</td>
<td></td>
</tr>
<tr>
<td>Propylthiouracil (PTU)</td>
<td>50 mg</td>
<td>Initial: 100–150 mg PO tid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maintenance: 50–100 mg PO bid</td>
</tr>
<tr>
<td>Methimazole (Tapazole)</td>
<td>5 mg</td>
<td>Initial: 20–30 mg PO bid or qd</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maintenance: 5–10 mg qd</td>
</tr>
<tr>
<td>Propranolol (Inderal)</td>
<td>10/40/80 mg</td>
<td>80 mg PO bid – 180 mg PO qid</td>
</tr>
<tr>
<td>Atenolol (Tenormin)</td>
<td>25/50/100 mg</td>
<td>25–100 mg PO qd</td>
</tr>
</tbody>
</table>

---

**Table 37.2 The Billewicz Index for hypothyroidism. Euthyroid if 30 or less; hyperthyroid if more than 30.**


<table>
<thead>
<tr>
<th>Symptom or sign</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diminished sweating</td>
<td>+6</td>
<td>-2</td>
</tr>
<tr>
<td>Dry skin</td>
<td>+3</td>
<td>-6</td>
</tr>
<tr>
<td>Cold intolerance</td>
<td>+4</td>
<td>-5</td>
</tr>
<tr>
<td>Weight increase</td>
<td>+1</td>
<td>-1</td>
</tr>
<tr>
<td>Constipation</td>
<td>+2</td>
<td>-1</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>+5</td>
<td>-6</td>
</tr>
<tr>
<td>Paresthesias</td>
<td>+5</td>
<td>-4</td>
</tr>
<tr>
<td>Deafness</td>
<td>+2</td>
<td>0</td>
</tr>
<tr>
<td>Slow movements</td>
<td>+11</td>
<td>-3</td>
</tr>
<tr>
<td>Coarse skin</td>
<td>+7</td>
<td>-7</td>
</tr>
<tr>
<td>Cold skin</td>
<td>+3</td>
<td>-2</td>
</tr>
<tr>
<td>Periorbital puffiness</td>
<td>+4</td>
<td>-6</td>
</tr>
<tr>
<td>Pulse &lt;75</td>
<td>+4</td>
<td>-4</td>
</tr>
<tr>
<td>Delayed relaxation, ankle jerk</td>
<td>+15</td>
<td>-6</td>
</tr>
</tbody>
</table>

² Siminoski K. Does this patient have a goiter? JAMA 1995;273:813–7. A survey of studies of thyroid palpation for goiter against the gold standard of thyroid ultrasound showed a likelihood ratio (LR) of 4 for palpable goiter and an LR of 0.4 for no goiter.
Low TSH levels in the setting of hypothyroidism are caused by rarely observed secondary (pituitary) or tertiary (hypothalamic) disease.

Measurement of free thyroxine (FT₄) confirms the diagnosis of hypothyroidism, but it may be normal early in the disease.

Up to 90% of patients with Hashimoto’s thyroiditis have high titers of antimicrosomal and antithyroglobulin antibodies. In a patient with a goiter and an elevated TSH, these tests are not necessary, but they can be helpful in confirming a diagnosis when TSH is borderline.

**Imaging studies**
- Hypothyroidism can usually be diagnosed clinically by history, physical exam, and laboratory tests.
- If there is a question of anatomy, a thyroid ultrasound can be done.
- There is almost never a need for a nuclear scan of the thyroid.

**Treatment**
- Thyroid hormone replacement with synthetic levothyroxine (T₄) is the standard treatment for hypothyroidism, regardless of etiology.
- The starting dose is 25–50 micrograms/day for typical adults, 12.5–25 micrograms/day in elderly people or in patients with cardiovascular disease. Younger, healthy adults can be started on full replacement doses of thyroxine immediately, but there is generally no need for rapid replacement.
- The average maintenance dose is:
  - 1.3–1.7 micrograms/kg per day in Hashimoto’s disease, where there is usually still some functioning thyroid tissue
  - up to 2.1 micrograms/kg per day in patients with full thyroidectomy
  - less than 1 microgram/kg per day in elderly patients.
- The biochemical goal is normalization of TSH. Symptoms may take weeks to months to abate.
- Thyroxine has a long half-life so TSH levels should not be checked until at least 4–6 weeks after initiation or any change in dose. Dosages are typically adjusted in increments of 12.5 to 25 micrograms. The eventual maintenance dose may differ from that required to initially normalize the TSH.
- The treatment goal is to return the TSH to normal with free T₄ at the lowest possible normal level.
- The major risk of overreplacement is osteoporosis and perhaps atrial fibrillation.
- Once the euthyroid state is achieved, TSH needs only to be checked annually.
- Some patients prefer to use older preparations of thyroid extract. These are dosed by iodine content rather than hormone content, so consistency of dosage is a problem.
- These older preparations contain l-tri-iodothyronine (T₃) as well as thyroxine. One small crossover trial demonstrated

Antimicrosomal and antithyroglobulin antibodies are present in both Hashimoto’s and Graves’ disease. These diseases occur in the same families and there are cases in which one disease progresses to the other. They may simply represent opposite ends of the clinical spectrum of autoimmune thyroid disease.

With normal thyroxine replacement doses, patients will often have their TSH return to normal but will have slightly elevated free T₄ levels. This occurs with approximately 25% of patients. Most patients with adequate replacement will have free T₄ levels in the mid to upper range of normal.

3 Greenspan SL, Greenspan FS. The effect of thyroid hormone on skeletal integrity. Ann Intern Med 1999; 130:750–8. While oversuppression of TSH decreases cortical bone mineral density (BMD), it is not clear if there is a concomitant rise in fracture rate. Appropriate doses of thyroxine may not significantly decrease BMD, but given the high prevalence of both osteoporosis and chronic thyroxine therapy in older women, measuring BMD is probably worthwhile in postmenopausal patients.
some clinical improvement with T₃ administration.⁴ Some experts feel that replacement of 50 micrograms of the daily dose of thyroxine with 5 micrograms of T₃ can be considered in the minority of patients who do not achieve satisfactory outcomes with appropriate doses of thyroxine.⁵

Subclinical hypothyroidism

- The prevalence of subclinical hypothyroidism (mildly elevated TSH with normal free T₄) may be as high as 10%.⁶
- These patients may be at risk for elevated cholesterol and progression to overt hypothyroidism.
- Data are scarce and conflicting about the benefit of treating subclinical disease.
- Patients with TSH > 10 mU/l or high titers of antithyroid antibodies have an increased risk of overt hypothyroidism⁷; some experts recommend treatment. Those with lower TSH levels and low antibody titers may be followed annually.⁵
- Screening for subclinical hypothyroidism (and thyroid disease in general) is controversial because there are no strong data about the benefits of treating subclinical disease; the American Thyroid Association⁸ recommends it and the American College of Physicians⁹ considers it optional.

Hyperthyroidism

Etiology

Common

- Graves’ disease and toxic multinodular goiter are by far the most common causes of hyperthyroidism. Graves’ disease occurs most often in younger women; toxic multinodular goiter is a disease of mid-life or later.

Less common

- Toxic uninodular goiter (toxic adenoma)
- Thyroiditis
  - Subacute thyroiditis
  - Chronic thyroiditis with transient thyrotoxicosis
  - Silent (lymphocytic) thyroiditis
  - Postpartum thyroiditis
- Iodide induced (iodide, iodine containing drugs, contrast media, amiodarone, lithium)

Rare

- Thyrotoxicosis due to an excess of TSH or TSH-like stimulators (choriocarcinoma, hydatidaform mole, embryonal cell carcinoma)
- Toxic thyroid carcinoma
- Exogenous thyroid hormone (factitious, iatrogenic)
- Toxic struma ovarii

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⁴ Bunevicius R, Kazanavicius G, Zalinkevicius R, Prange AJ Jr. Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism. N Engl J Med 1999;340:424–9. 33 patients (half with Hashimoto’s, half with thyroid cancer) were followed for five weeks on their typical thyroxine dose, and then for five weeks with 50 micrograms of the thyroxine dose replaced with 5 micrograms of T₃. TSH, cholesterol, triglycerides and blood pressure were similar in both protocols. In the T₃ protocol, there were small but significant improvements on a battery of neuropsychological tests and in sex hormone binding globulin (an index of thyroid function).


⁷ Vanderpump MPJ, Tunbridge WMG, French JM et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol 1995;43:53–68. 2779 British adults were evaluated for thyroid and cardiac disorders. The odds ratio for developing overt hypothyroidism in women after 20 years was 8 for elevated TSH or positive antibodies and 32 for both. In a related paper, the same investigators reported no association between subclinical hypothyroidism and the development of ischemic heart disease.

⁸ Ladenson PW, Singer PA, Ain KB et al. American Thyroid Association Guidelines for Detection of Thyroid Dysfunction. Arch Intern Med 2000;160:1573–8. Screening with TSH beginning at age 35 and every five years thereafter in all adults, particularly women, is recommended.

Diagnosis

History

- Hyperthyroidism represents a general increase in metabolic rate. The clinical presentation is highly variable.
- Classic symptoms include hyperkinetic movements, heat intolerance, weight loss, increased appetite, fatigue, palpitations, and changes in eye appearance. See Table 37.2.
- Patients may also note insomnia, scant menses, and infertility.
- In elderly patients there may be atypical or vague symptoms. Anorexia and wasting are often prominent.

Physical exam

- Findings include goiter, tachycardia, atrial fibrillation, hair loss, lid lag, lid retraction, proptosis, and fine hand tremor.
- The characteristics of goiter may vary, depending on the etiology.
  - Graves’ disease: diffusely enlarged, soft, and vascular. There is often a bruit over the gland
  - Toxic multinodular goiter: diffusely enlarged, nodular, and non-tender
  - Toxic adenoma: usually non-tender with one focal area of enlargement
  - Subacute thyroiditis (de Quervain’s): mildly enlarged and tender
  - Chronic thyroiditis: moderately enlarged and non-tender

Laboratory tests

- TSH is low or undetectable in hyperthyroidism. An elevated free T4 is confirmatory. Free T3 doesn’t need to be measured unless free T4 is normal.
- In the rare cases of idiopathic TSH excess, TSH levels are elevated.
- Antithyroglobulin and antimicrosomal antibodies are common in Graves’ disease (as they are in Hashimoto’s disease), but are not necessary to obtain if the clinical features of Graves’ are present.
- The absence of thyroid autoantibodies may differentiate toxic multinodular goiter from Graves’ disease.

Imaging studies

- A radioactive iodide uptake scan is indicated when the etiology of the patient’s hyperthyroidism is not clearly due to Graves’ disease or toxic nodular goiter.
- Radiiodide uptake is increased in true hyperthyroidism (Graves’ disease, toxic nodular goiter) and decreased in non-hyperthyroid thyrotoxicosis (thyroiditis or drugs).
- Uptake is decreased for 2–4 weeks following ingestion of thyroxine, antithyroid drugs, iodides, or iodinated contrast material. Therefore, propylthiouracil or methimazole should not be started until after the thyroid scan is done.
Ultrasound of the thyroid can assess the architecture of the gland (diffuse enlargement versus nodularity).

Treatment

Relief of symptoms

- Tachycardia, tremor, sweating, and agitation can be treated with β blockers. Propranolol is the traditional agent, but longer acting agents (atenolol, metoprolol) appear to be equally effective.
- Potassium iodide is reserved for relief of symptoms in patients with severe hyperthyroidism who are in need of rapid correction.

Graves’ disease

- The three treatment choices – antithyroid medication, radioiodine therapy, and surgery – are equally effective in returning the patient to the euthyroid state within 4–8 weeks. The treatments differ in complications, relapse rates, and incidence of hypothyroidism.

Antithyroid medications

- The thiocarbamide agents – propylthiouracil (PTU), carbimazole, and methimazole – reliably inhibit hormone production. These medications are the most common initial treatments in Europe.
- PTU inhibits the peripheral conversion of T₄ to T₃ and may achieve the euthyroid state faster, but methimazole has more convenient dosing.
- The patients most likely to do well on antithyroid drugs are those with mild disease and small goiters, but this is difficult to predict.
- Typically, patients are treated for 18–24 months and then evaluated off medications. Thirty to sixty percent of patients relapse, but the remainder are cured. Patients who relapse rarely remit with a second course of therapy and need another form of treatment.
- Dosage is titrated to normalize free T₄, since TSH levels may remain suppressed for months after a euthyroid state is achieved.
- An alternative regimen is to use a higher dose of a thiocarbamide (not titrated to T₄ level) plus thyroxine. The thyroxine serves to prevent hypothyroidism, but may also prevent release of thyroid antigens by keeping TSH suppressed. There is evidence both for and against this “block-replace” regimen.
- Thiocarbamides are also used to establish the euthyroid state prior to definitive treatment with radioactive iodide or surgery.
- Of those patients receiving thiocarbamide agents, approximately 15% will become hypothyroid over the next 15 years.

Unlike hypothyroidism, treatment for hyperthyroidism is diagnosis dependent.

10 Torring O, Tallstedt L, Wallin G et al. Graves’ hyperthyroidism: treatment with antithyroid drugs, surgery, or radioiodine: a prospective randomized study. J Clin Endocrinol Metab 1996;81:2986–93. 60 young adults (20–34 years) were randomized to medical or surgical therapy. 119 older adults (35–55 years) were randomized to medical, surgical or 131I treatment. All treatments achieved euthyroid state at six weeks. Risk of relapse at four years was:
- Medical therapy: young 42%; older 34%
- Radioiodine therapy: 21%
- Surgery: young 3%; older 8%

11 Maugendre D, Gatel A, Campion L et al. Antithyroid drugs and Graves’ disease – prospective randomized assessment of long-term treatment. Clin Endocrinol 1999;50:127–32. Patients with Graves’ disease were treated with carbimazole (the pro-drug form of methimazole) for 18 or 42 months. Two years after discontinuation there was no significant difference in relapse rates (36% v 29%).


Minor side effects include rash and leukopenia. The most serious side effects, agranulocytosis and hepatic necrosis, are rare (probably <0.1%) but it is not clear if routine laboratory monitoring is beneficial.

**Radioiodine therapy**
- Oral radioactive iodide ($^{131}$I) is the most common initial treatment for Graves’ disease in North America.
- Pre- and post-treatment with antithyroid medications is necessary for patients with severe hyperthyroidism, although PTU can reduce the effectiveness of $^{131}$I. Pretreatment is probably not necessary for mild to moderate disease.
- The main drawback to radioiodide therapy is the high incidence of postablative hypothyroidism: approximately 25% of patients receiving $^{131}$I will become hypothyroid, 40% of which will be permanent. After treatment, an additional 3–4% of patients per year will require thyroxine replacement.
- $^{131}$I is contraindicated in pregnancy and lactation, although teratogenicity has never been established. It appears to worsen Graves’ ophthalmopathy, especially in patients who smoke.
- The standard ablative dose is 5–10 millicuries (mCi), based on thyroid size. This radiation dose is less than a standard radiograph and there is no increased risk of cancer.

**Surgery**
- Subtotal thyroidectomy, although no longer commonly performed, is an option in patients unable to receive antithyroid drugs.
- Complications include hoarseness from damage to the recurrent laryngeal nerve, hypoparathyroidism, and hypothyroidism.

**Toxic nodular goiter**
- Treatment is usually with radioactive iodide at a higher dose (15–30 mCi) than that given for Graves’ disease.
- Antithyroid medications are used to achieve a euthyroid state, but cannot be expected to yield a cure.
- β Blockers are helpful for symptomatic relief.
- Postablative hypothyroidism occurs less frequently than with Graves’ disease.
- Treatment of toxic adenoma (toxic uninodular goiter) can be either with radioiodide or surgery.

**Thyroiditis**
- Treatment is symptomatic. Most patients respond to aspirin, with more severe cases requiring prednisone for relief.
- β Blockers can be used if hyperthyroidism is symptomatic.

**Iodide induced**
- Treatment is to remove the offending agent and treat symptoms.
Subclinical hyperthyroidism
- The prevalence of subclinical hyperthyroidism (undetectable TSH with normal free T₄ and T₃) may be as high as 1%.
- These patients may be at risk for atrial fibrillation, osteoporosis, and progression to overt hyperthyroidism.
- There are no randomized controlled trials of treatment of subclinical hyperthyroidism. One observational study hints at a benefit in preventing atrial fibrillation.
- Patients with goiter or Graves’ ophthalmopathy should probably be treated. In the absence of symptoms, these patients should probably be re-evaluated every 6–12 months.
- The benefit of screening for subclinical hyperthyroidism is controversial because of the lack of efficacy data, but the American Thyroid Association recommends it and the American College of Physicians considers it optional.

Thyroid nodule
Epidemiology
- Solitary nodules are extremely common, both palpable and non-palpable (picked up on imaging studies done for other reasons). About 5% of these nodules will be malignant.
- Benign nodules consist of follicular adenomas, colloid adenomas, or cysts. The adenomas may be hyperfunctioning (hot) or hypofunctioning (cold). A cold nodule raises the possibility of carcinoma.
- The majority of thyroid cancers are slow, locally growing papillary tumors. Follicular cancers metastasize more frequently. Anaplastic cancers are highly malignant. Medullary thyroid cancer and pheochromocytoma can be part of multiple endocrine neoplasia syndromes 2A and 2B.

Diagnosis
History, physical, and labs
- Signs and symptoms of hyper- and hypothyroidism
- Recent changes in the size of the gland
- Size, consistency, and mobility of the nodule
- Free T₄, TSH
- T₃ (if T₄ is normal and the patient is clinically hyperthyroid)

Diagnostic studies
- Fine needle aspiration (FNA) provides the most information about the nature of a thyroid nodule and is usually the initial step in evaluation.
- FNA is always performed if:
  - the nodule is > 1 cm (all palpable nodules)
  - there is a history of upper body radiation
  - there is a family history of thyroid cancer
  - there are any suspicious features on ultrasound.
- Patients with none of these features may be followed every 6–12 months with ultrasound.
Thyroid ultrasound can be performed if there is any question about the underlying anatomy of the gland. Often, what appears to be a solitary lesion on exam turns out to be a prominent nodule in a diffusely nodular gland.

Radioiodide uptake scan can distinguish hot from cold nodules, but typically does not avoid the need for FNA.

Treatment
- Malignant nodules are treated with excision, radiation, or chemotherapy as determined by staging.
- Benign nodules may be treated with thyroxine suppressive therapy, but the effect is small.\textsuperscript{21}
- Some experts suggest a trial of thyroxine therapy in younger patients with repeat ultrasound, and perhaps FNA, in one year. If the nodule has decreased in size and the cytology remains benign, thyroxine can be continued.
- For older patients, the risks of suppressive therapy may outweigh the small benefits.
- Surgical excision may be required for nodules that do not shrink or with cytology that is equivocal.
- Cystic nodules are often cured by the diagnostic FNA.

\textsuperscript{21} Zelmanovitz F, Genro S, Gross JL. Suppressive therapy with levothyroxine for solitary thyroid nodules: a double-blind controlled clinical study and cumulative meta-analyses. J Clin Endocrinol Metab 1998;83:3881–5. A meta-analysis of small prospective studies of thyroxine replacement (total N=242 treated, 171 controls) concluded that thyroxine treatment was associated with decreased nodule volume in 17% of patients and may inhibit further growth in another 10%.
38 Tuberculosis and PPD testing
Jennifer Schelker

Epidemiology

- Five to ten percent of the US adult population is infected with *Mycobacterium tuberculosis* (MTB).
- There were 19,855 cases of active tuberculosis (TB) reported to the Centers for Disease Control and Prevention in 1997, which is a 25% decrease from 1992 when the resurgence of TB in the US had reached its peak.
- Foreign born persons now account for 39% of cases.
- The proportion of new cases with drug resistance has substantially decreased. In 1997, 7.6% were resistant to at least INH and 1.3% to at least INH and rifampin.
- Tuberculosis case fatality rates are minimal in adults but increased in elderly people (18%) and in patients with multidrug resistant TB (MDRTB) (35–85%).

Latent infection

**Diagnosis**

**Purified protein derivative (PPD) skin testing**

- Intradermal injection of 0.1 cc (5 tuberculin units) of tuberculin (protein antigens from MTB culture extracts)
- The test should be read in 48–72 hours.
- Results are based only on the amount of induration, not erythema. They should be reported as millimeters of induration.
- Results should be read only by trained readers. Patients should not be allowed to read their own skin tests.

**Detection of Induration in a PPD Test; Comparison of Patients’ and Physicians’ Interpretations**

<table>
<thead>
<tr>
<th>Size</th>
<th>Examiner</th>
<th>PPD+</th>
<th>PPD−</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 mm</td>
<td>Patients</td>
<td>68%</td>
<td>32%</td>
</tr>
<tr>
<td></td>
<td>Professionals</td>
<td>87%</td>
<td>13%</td>
</tr>
<tr>
<td>13 mm</td>
<td>Patients</td>
<td>89%</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td>Professionals</td>
<td>97%</td>
<td>3%</td>
</tr>
</tbody>
</table>

**Characteristics of the PPD test**

- Sensitivity is less than 100% and depends on the immunologic status of the patient, the amount of time since initial infection, and factors related to the proper administration and reading of the test.
- Specificity is variable, generally <95%, and depends mainly on the prevalence of non-tuberculous mycobacterial infection in the area.
- Infections with these other Mycobacteria produce a smaller reaction (4–12 mm) than those due to MTB.
- The larger the reaction size, the more specific it is for MTB.
- Bacillus Calmette-Guérain (BCG) vaccination can similarly produce false positive results.

Koch’s Postulates and the discovery of mycobacterium tuberculosis

“To prove that tuberculosis is a parasitic disease, that it is caused by the invasion of bacilli,...it was necessary to isolate the bacilli from the body; to grow them in pure culture until they were freed from any disease-product of the animal organism which might adhere to them; and, by administering the isolated bacilli to animals, to reproduce the same morbid condition which, as known, is obtained by inoculation with spontaneously developed tuberculous material.”


4 Ozuah PO, Burton W, Lerro KA, Rosenstock J, Mulvihill M. Assessing the validity of tuberculin skin test readings by trained professionals and patients. *Chest* 1999;116:104–6. A calibrated rubber model was used to test 233 patients and 75 physicians and nurses in their ability to detect the presence of 0, 3, 7, and 13 mm of induration. The results for the 7 and 13 mm sites are reported in the table on the left.

An initially infected host may take up to 12 weeks before developing a hypersensitivity reaction. Immunity may wane after many years of infection.

The response to BCG is often < 10 mm and starts to wane as early as 18 months after the vaccination.

Most PPD positive patients from high risk areas should be treated by ignoring a remote history of BCG vaccination.

Given the 5–10% prevalence of latent TB in the US and assuming 100% sensitivity and 95% specificity for the PPD test, the positive predictive value of skin testing is only about 60%.

**Whom to screen**

- Testing the general population with PPD is not useful. It is recommended only for those at high risk of infection and active disease (patients in whom treatment would be given if found to be PPD positive). Otherwise healthy persons with TB infection have at most a 5–10% lifetime risk of active disease, but much of this risk is in the first few years after acquiring infection. Therefore, candidates for screening and treatment include patients recently infected with MTB or with the following other conditions associated with increased risk:
  - Close contacts of newly identified cases of active TB.
  - HIV positive patients.
  - Persons with medical conditions known to increase the risk of active disease if infection occurs.  
  - Adult immigrants who have arrived within the last five years from developing countries.
  - Children or young adult immigrants, regardless of time since arrival.
  - Those with fibrosis on CXR consistent with prior active TB.
  - Residents and employees of high risk, crowded institutions (hospitals, prisons, nursing homes, homeless shelters).
  - IV drug abusers and other identifiable high risk groups as defined by local public health agencies.

**Serial PPD testing**

- In a serial test done < 2 years after the first PPD injection, a skin test conversion is defined as an increase in reaction size of at least 10 mm. Serial testing lowers the test's specificity due to enhancement of non-specific crossreactivity. Testing all patients at regular intervals would have a low yield; serial testing should be reserved for individuals at significant risk for repeated exposure to TB:
  - healthcare workers (test every year)
  - homeless persons
  - active drug users
  - those in high risk congregate settings
  - HIV positive patients at risk for continuing exposure.

Consider retesting HIV positive patients with a previously negative PPD if they have evidence of improved immune function on antiretroviral therapy.

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7 Patients with immunosuppression, cancer, endstage renal disease, diabetes, silicosis, malnutrition, substantial rapid weight loss, gastrectomy.

**Incidence of Active Tuberculosis in PPD Positive Patients**

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Active TB cases/1000 person yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1º TB infection less than 1 year ago</td>
<td>13</td>
</tr>
<tr>
<td>1º TB infection 1–7 years ago</td>
<td>1.6</td>
</tr>
<tr>
<td>HIV infection</td>
<td>35–162</td>
</tr>
<tr>
<td>Injection drug use and HIV seronegative</td>
<td>10</td>
</tr>
<tr>
<td>Evidence of prior TB on radiograph</td>
<td>2–14</td>
</tr>
<tr>
<td>Underweight by 15% or more</td>
<td>2.6</td>
</tr>
</tbody>
</table>

8 New immigrants are at increased risk for active disease. Younger immigrants are more likely than older immigrants to have been infected recently in their native country and are thus at increased risk for active disease for the first several years after arrival in the US. McKenna M, McCray E, Onorato I. The epidemiology of tuberculosis among foreign-born persons in the US, 1986–1993. N Engl J Med 1995;332:1071–5.

9 This does not include calcified granuloma, Ghon complex (calcified peripheral nodule plus a calcified hilar lymph node), or apical pleural thickening, which represent prior infection but not prior active disease.
**The booster phenomenon**
- Patients who were vaccinated with BCG, those exposed to non-tuberculous mycobacteria, or those with a remote infection can lose reactivity to PPD after several years. This phenomenon can occur at any age, but is more common with increasing age.
- These patients can develop a positive PPD from repeated testing due to restimulation of waned immunity. This phenomenon is called the *booster effect*. Often this results in the incorrect interpretation of this positive result as a new conversion.
- In patients who require serial testing every 1–2 years, initial two step testing can prevent the reading of a booster effect as a new conversion.\(^\text{10}\)

**Testing for anergy**
- Anergy skin testing is unreliable; it should not be used to make decisions regarding preventive treatment.\(^\text{11}\)
- Without any other reliable method of determining anergy, physicians may make a clinical judgment as to risk of prior TB exposure in PPD negative, HIV positive patients.

**Interpretation of the PPD test**
- **5 mm** induration is considered positive for those with high probability for infection or at high risk for active disease if infected.
  - HIV positive patients (5–10% annual risk of reactivation)
  - Close contacts of newly identified cases
  - Persons with fibrosis on chest radiograph consistent with healed, prior active TB (0.2–1.4% annual risk of reactivation)\(^\text{12}\)
  - Prolonged high dose corticosteroid treatment or other immunosuppressive treatment.\(^\text{13}\)
- **10 mm** cutoff for those at moderately increased risk.
  - Silicosis (30% develop active TB within five years of infection)
  - Cancer patients
  - Endstage renal failure
  - Diabetes mellitus, particularly poorly controlled, insulin requiring (10–20% lifetime risk)
  - Substantial weight loss, gastrectomy, malnutrition
  - Immigrants from developing countries
  - Intravenous drug abusers
  - Residents and employees of high risk congregate settings.
- **15 mm** cutoff for those at low risk.
  - Populations at low risk for infection should not be routinely screened; however, if they are tested, a cutoff of 15 mm is recommended.

\(^{\text{10}}\) Two step testing elicits the boosted response by applying a second PPD 1–3 weeks after an initial negative PPD test. If the second test is positive, it is a boosted response indicative of remote infection or BCG vaccination.

\(^{\text{11}}\) Chin DP, Osmond D, Page-Shafer K. Reliability of anergy skin testing in persons with HIV infection. Am J Respir Crit Care Med 1996;153:1982–4. Fifty HIV positive, PPD positive patients were followed with serial PPD and anergy testing. The mumps antigen test was positive in 39% of the patients who had a false negative tuberculin test. In cases like these, PPD negative, non-anergic patients who were truly infected with MTB would be considered uninfected and not offered preventive treatment.

\(^{\text{12}}\) Active disease must first be carefully ruled out in these patients. In some, initial therapy for possible active disease is appropriate pending AFB stain, sputum culture, and follow up CXR results.

\(^{\text{13}}\) Data are inadequate to determine the dosage and length of steroid treatment that increases the risk of reactivation, but the American Thoracic Society (ATS) recommends >15 mg per day for >2–3 weeks as the cutoff.
Treatment of latent TB infection (Prophylaxis against active TB)\textsuperscript{6}

Whom to treat

- All PPD positive patients identified as high risk for TB infection and active disease who have thus been selected for screening are candidates for treatment, regardless of age.
- For those patients at low risk who are found to be PPD positive the benefit is small; however, treatment may be considered if the risk of therapy is also estimated to be small.

Prophylaxis with isoniazid (INH)

Benefit: prevention of active disease

- A 12 month regimen of daily INH is about 90\% effective in preventing active disease in patients who are completely compliant. However, results based on intention to treat analyses are less impressive, with a 75\% protective efficacy for the 12 month regimen and 65\% efficacy with a six month INH regimen.\textsuperscript{14} Therefore, for patients who are at higher risk for active TB and who are likely to be compliant with a longer duration of treatment, then a 9–12 month regimen is probably cost effective.

- The American Thoracic Society and the Centers for Disease Control now recommend nine months of INH.\textsuperscript{6} Six months of INH is considered a less optimal but acceptable alternative.

Risk: hepatitis

- Asymptomatic increases in liver function tests (LFTs) occur in 10–20\% of patients taking INH, but return to normal as treatment continues in most patients.
- Rates of hepatitis requiring discontinuation of therapy increase with alcohol use and age as follows.\textsuperscript{15}

<table>
<thead>
<tr>
<th>Age</th>
<th>Risk of hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–34</td>
<td>\textsim .3%</td>
</tr>
<tr>
<td>35–49</td>
<td>\textsim .1.2%</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>\textsim .2.3%\textsuperscript{15}</td>
</tr>
</tbody>
</table>

- Latest estimates for fatal hepatitis are 1–10 cases per 100,000 persons\textsuperscript{16} and not better defined because of significant underreporting.
- Absolute contraindications to INH include previous serious adverse reactions and acute or unstable liver disease.
- It is unclear whether routine prophylaxis should be begun during pregnancy or after delivery. However, if the patient is newly infected with a documented conversion, prophylaxis should begin after the first trimester. If the patient is HIV positive, treatment should begin without delay.\textsuperscript{6,17}

Prophylaxis with short course rifamycin containing regimens

- In HIV positive patients, there is comparable efficacy between a two month regimen of daily pyrazinamide (PZA) and rifampin, and nine months of INH.\textsuperscript{18}

\textsuperscript{14} International Union Against Tuberculosis Committee on Prophylaxis. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. Bull WHO 1982;60:535–64.

This is the only randomized study designed to compare different durations of INH treatment. 27,000 participants with fibrotic pulmonary lesions consistent with inactive TB were assigned to placebo or three, six or 12 month INH regimens. The five years incidence rates of tuberculosis were 1.43\% with placebo and 1.13\%, 0.5\% and 0.36\% with the three, six, and 12 month regimens, respectively.\textsuperscript{15}


In this meta-analysis, the selection of studies was restricted to include only those that monitored patients with monthly follow up according to current guidelines.

\textsuperscript{17} It is important to rule out active TB in PPD positive pregnant women.
- A CXR with appropriate shielding should be performed after the 12th week of gestation.
- If symptoms of active disease are present, obtain radiograph regardless of the week of gestation.
- The risk of perinatal transmission of TB to the child outweighs the risk of side effects from TB medications; multidrug treatment is indicated in a pregnant patient with active TB.
- INH, rifampin, and ethambutol have minimal fetal toxicity.
- The effects of PZA during pregnancy are not known.


Gordin F, Chaisson RE, Matts JE et al. Rifampin and pyrazinamide vs isoniazid for prevention of tuberculosis in HIV-infected persons. JAMA 2000;283:1445–50. 1583 patients were randomized to two months of rifampin and pyrazinamide or 12 months of INH. All patients were HIV positive and PPD positive; only 7\% had AIDS. After a median follow

Continued
• Trials of two months of PZA and rifampin in HIV negative patients are now under way; presently it is considered an acceptable alternative in HIV negative patients.
• Rifampin is contraindicated in HIV positive patients taking protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs); regimens with rifabutin are preferred.
  —For those patients receiving protease inhibitors or NNRTIs, a two-month regimen of rifabutin and PZA is probably as effective as regimens that include rifampin.
  —The use of rifabutin and PZA usually requires dosage adjustment of both rifabutin and antiretroviral agents; this should be managed in consultation with a specialist.
  —Use of rifamycins with PI/NNRTI combinations is not recommended, as the effects may be unpredictable.
  —Rarely, rifamycins cause leukopenia or thrombocytopenia.
  —Rifamycins and PZA may also cause hepatitis.

Monitoring of patients on treatment
• Patients should be educated about potential side effects of the drug regimen. They should be instructed to stop the medication and contact their doctor immediately if they develop easy bruising, bleeding, jaundice, abdominal pain, anorexia, fever, fatigue, nausea, or vomiting.
• Patients should have follow up visits at least monthly to assess for symptoms or signs of hepatotoxicity.
• If receiving the rifampin/PZA regimen, follow up should be at two, four, and eight weeks.
• Baseline and monthly LFTs are not routinely indicated, but should be performed in all patients with a history of HIV infection, liver disease, alcoholism, or who are pregnant (with follow up until three months post partum).
• For patients with symptomatic hepatitis or those with transaminase levels greater than 3–5 times normal, INH should be discontinued.
• Consider following hemograms in patients on rifamycins if pregnant, HIV positive, or with a history of cytopenias.
• For persons at high risk for developing active TB or those whose compliance is questionable (alcoholics, psychiatric patients), directly observed preventive therapy (DOPT) should be considered. With DOPT, patients visit a nurse to take the medication and receive some incentive for participating. DOPT regimens often use higher doses at greater intervals, for example, isoniazid 900 mg twice a week.

Management of close contacts
• Those with a positive PPD test (>5 mm) and no history of PPD reaction in the past should be considered recently infected and receive preventive therapy.
• Immunocompetent contacts with a history of a previous positive PPD test usually do not need preventive therapy.
Those with an initial negative PPD test should be followed closely and have the test repeated in three months. If the test is then positive, they should be treated. Young children, HIV positive patients, and other immunocompromised patients should be considered for immediate preventive therapy, regardless of an initial PPD negative result. Management of close contacts of INH resistant and MDRTB cases is based on expert opinion. For INH resistant infections, two months of rifampin and PZA is recommended. For MDRTB infections, high risk patients should be treated with multidrug therapy guided by \textit{in vitro} susceptibility testing. Untreated patients should be followed closely for two years.

**Active tuberculosis**

**Diagnosis**

\textit{History and physical exam}

- Symptoms are insidious and chronic
- \textit{Systemic complaints}: weight loss, low grade fevers, night sweats
- \textit{Respiratory symptoms}: chronic cough, often with scant, bloodstreaked sputum, and/or pleuritic chest pain
- Findings on physical exam of the lungs are often minimal. Rales that are heard only after coughing are characteristic.
- Extrapulmonary TB can involve any organ system (especially the lymph nodes, meninges, liver, and bone). Almost half of AIDS patients with TB have extrapulmonary disease.
- Miliary disease develops from hematogenous dissemination, usually associated with primary infection, and often presents as persistent fever with anemia and splenomegaly.

**Diagnostic tests**

\texttt{Acid fast bacilli (AFB) sputum smear}

- Three to six morning specimens should be collected on separate days. There is no advantage to more than six specimens.
- Sensitivity is 50–80%. Sensitivity is lower for miliary disease (25–50%) and higher for cavitary disease.\textsuperscript{19,20}

\texttt{Sputum culture}\textsuperscript{19}

- Sensitivity is 80–85%, specificity is approximately 98%.
- New commercial broth culture systems can decrease the time to identification of a positive culture from 3–8 to 1–3 weeks.

\texttt{Rapid diagnostic tests for MTB RNA or DNA}\textsuperscript{19}

- Nucleic acid amplification methods may be used to confirm that mycobacteria detected by AFB smear are \textit{Mycobacterium tuberculosis}.
- Specificity of these tests is approximately 95%.
- Sensitivity is approximately 98% when the sample is AFB positive.

\begin{table}
\centering
\begin{tabular}{|c|c|c|}
\hline
\textbf{Test} & \textbf{Sensitivity} & \textbf{Specificity} \\
\hline
AFB stain & 68% & 90% \\
DAT* & 84% & 60% \\
On AFB + samples & 96% & 40% \\
On AFB + to + + + + samples & 87% & 70% \\
Overall & & \\
\hline
\end{tabular}
\caption{Test sensitivities and specificities for tuberculosis diagnosis.}
\end{table}


\textsuperscript{20} Gallina M, Troupioti P, Rocco G, Sensalari, G, Libanori E. Predicting culture results for mycobacterium tuberculosis complex: amplified mycobacterium tuberculosis direct test and acid-fast bacilli microscopy. Chest 2000;118: 28–32. Analysis of 462 sputum and bronchoscopy samples from 310 patients in one Italian hospital. MTB was cultured from 33% percent of samples. Results listed below.
• Sensitivity drops to 48–53% when performed on samples with negative AFB stains.
• These data were obtained from research laboratories and may not reflect results from clinical laboratories.20

Chest radiograph (CXR)
CXR may not reliably distinguish between primary and reactivation disease.
• Primary TB21
  —A minority of patients have a normal CXR.
  —Half of patients have pulmonary consolidation, usually unifocal. The middle and lower lobes of the lungs are involved more often than the upper lobes. When the upper lobe is involved it is usually in the anterior segment.
  —Involvement of atypical sites, including the apical and posterior segments of the upper lobe, is seen in many patients, but rarely occurs without involvement of other typical sites.
  —Other possible findings include pleural effusion, lymphadenopathy, and cavitation.
• Reactivation TB22
  —Radiographs are very rarely normal.
  —Residua of primary disease may be present (calcified nodules or lymph nodes, blunting of the costophrenic angles).
  —Most patients have involvement of more than one lobe.
  —The apical and posterior segments of the upper lobes are the ones most often affected.
  —Involvement of atypical sites, including anterior upper lobe or basilar sections of the lower lobe, is seen in many patients, but rarely occurs without involvement of other typical sites.
  —Cavitation occurs in about half of patients.
  —Lymphadenopathy occurs in a small percentage of patients.
  —Apical pleural thickening is a common finding; pleural effusion occurs in a minority of patients.

PPD skin test
• The sensitivity is 75% in patients with active disease.19

Bronchoscopy
• In the absence of positive sputum smears, one can treat empirically, following for clinical and CXR response until culture results return.
• When the differential diagnosis is complex (as is often the case in AIDS patients) or when there is no response to therapy, bronchoscopy can be performed to establish a diagnosis.

Tissue biopsy
• Because of difficulty culturing MTB from body fluids, biopsy is usually necessary to make the diagnosis of extrapulmonary TB.
Treatment
- All patients should be counseled and offered HIV testing.
- A pulmonary consultation is recommended for all new cases of active TB.
- Isolation: infectivity is greatest among those with positive AFB smears, productive cough, cavitary disease, and inadequate treatment. The following patients with AFB positive sputum smears should be hospitalized and placed in respiratory isolation.
  - Patients addicted to drugs or alcohol
  - Patients who are unwilling to wear a mask or to cover their mouths while coughing
  - Patients who live in a congregate setting or with children or with immunocompromised adults or with healthcare workers.
- Every patient should be considered for directly observed therapy, in which patients receive payment for taking their pills in front of a supervisor.

Choosing a drug regimen
- Multidrug therapy is necessary to prevent resistant strains.
- If the probability of INH resistance is low, initial therapy can be daily I/R/P; otherwise, ethambutol or streptomycin must be added.23
- Treatment of suspected or confirmed multidrug resistant TB should be decided by a specialist.
- All patients should have a baseline hemogram, electrolytes, and LFTs. They should be advised about common adverse reactions and have a monthly medical interview to elicit these symptoms.
- Monthly sputum samples should be collected to assess conversion of smears and cultures. Patients with continued symptoms or positive sputum smears after two months should be carefully re-evaluated by an expert. Extended treatment is required in patients who are slow to clear their sputum, who have HIV or extensive pulmonary disease.
- Never add a single drug to a failing regimen.
- Once drug susceptibility is known, the drug regimen should be re-evaluated.
- For pansensitive TB, after two months of I/R/P, the preferred regimen is daily I/R for four more months.
- If PZA is not used due to a contraindication, I/R for nine months is also highly successful for pansensitive organisms.
- For INH resistant cases, rifampin, ethambutol, and PZA should be continued for six months.
- In patients with negative sputum smears and cultures and low probability for drug resistance, a four month regimen of I/R is acceptable.24
- Extrapulmonary TB should be managed using the same principles and drug regimens described above for pulmonary TB.

---

that a diagnostic test would be less sensitive in patients with a greater burden of disease. This unusual phenomenon occurs because progression of TB produces secondary effects (malnutrition and immunosuppression) that alter the outcome being measured (induration caused by delayed-type hypersensitivity to tuberculin).

23 There is low probability of drug resistance if there is <4% INH resistance in the community, the patient has had no previous treatment with TB medications, is not from a country with prevalent drug resistance, and has had no known exposure to a drug resistant case.

I = isoniazid (INH)
R = rifampin
P = pyrazinamide (PZA)
E = ethambutol

24 Gelband H. Regimens of less than six months for treating tuberculosis (Cochrane Review). In: The Cochrane Library, Issue 1. Oxford: Update Software, 2000. A review of seven randomized, controlled trials in which there were at least two treatment arms with different durations of therapy, and at least one treatment arm lasting for less than six months. Relapse rates were consistently higher with shorter regimens. Even so, relapse rates were low in all groups: 1–9% in the longer regimens and 1–10% in the shorter regimens (except for one trial where the shorter regimen had a relapse rate of 18%). The studies were heterogeneous with regard to treatment regimen and patient population. None of the studies used intention to treat analyses.
Treating HIV positive patients
Concurrent treatment with antimycobacterials and antiretrovirals should be managed by a pulmonary or infectious disease specialist, given the potential for drug interactions.

**Table 38.1 Agents for tuberculosis.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Usual dose</th>
<th>Adverse effects, comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid (INH)</td>
<td>3–5 mg/kg</td>
<td>300 mg PO qd</td>
<td>Hepatitis; peripheral neuropathy – give with vitamin B&lt;sub&gt;6&lt;/sub&gt; 25 mg PO qd; drug fever; rash; mood disorders; increases phenytoin and disulfiram levels.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>900 mg PO biw</td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td>10 mg/kg</td>
<td>600 mg PO qd</td>
<td>GI upset, hepatitis, rash, rarely thrombocytopenia. Many drug interactions (see text). Turns secretions orange. May permanently stain soft contact lenses.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>600 mg PO biw</td>
<td>Intermittent therapy may be associated with a flu-like syndrome and, rarely, acute renal failure.</td>
</tr>
<tr>
<td>Pyrazinamide (PZA)</td>
<td>15–20 mg/kg</td>
<td>2 g PO qd</td>
<td>GI upset, hepatitis, hyperuricemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3–3.5 g PO biw</td>
<td></td>
</tr>
<tr>
<td>Ethambutol</td>
<td>15 mg/kg</td>
<td>1 g PO qd</td>
<td>Optic neuritis (rare, dose related). Patients need a baseline ophthalmologic exam and should report any change in vision.</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>5 mg/kg</td>
<td>300 mg PO qd</td>
<td>GI upset, rash, hepatitis, thrombocytopenia, neutropenia, myalgias, arthralgias, uveitis. Many drug interactions. Dosage adjustments often required.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>300 mg PO biw</td>
<td></td>
</tr>
</tbody>
</table>
The common cold

Epidemiology

- Viral rhinitis is the most common upper respiratory infection (URI), with an incidence of 2–3 colds per adult per year in the United States.  
- Transmission occurs by aerosol and direct contact; the latter is the most efficient method of spread. The virus can survive for hours on hard surfaces like wood or formica.  
- There are more than 200 strains from six virus families. Rhinovirus (15–40%) and coronavirus (10–20%) account for the majority of colds in adults.

Diagnosis

- The symptoms are rhinorrhea, nasal congestion, cough, sneezing, and sore throat. Systemic signs like fever, myalgia, and headache are mild or absent.  
- Because the therapies for each differ, it is important to distinguish between a “runny” and a “stuffy” nose.

Treatment

- Treatment should be directed at relief of individual symptoms. Many combinations of five basic drug classes exist. Symptoms should be targeted one by one and combinations containing superfluous drugs avoided.
  
  - Cough suppressants
  
  - Analgesics/antipyretics
  
  - Decongestants: oxymetazoline and pseudoephedrine. There is a 13% reduction in symptoms of nasal congestion with use of these agents after a single dose. These agents are α adrenergic agonists.
  
  - Mucolytics: guaifenesin, potassium iodide, or nasal saline for thick postnasal discharge.
  
  - Antihistamines: for rhinorrhea, sneezing, and postnasal drip.

Percentage of Patients with ≥50% Relief of Common Cold Symptoms after Use of First Generation Antihistamines  

<table>
<thead>
<tr>
<th>Relief from rhinorrhea</th>
<th>Relief from sneezing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 (%)</td>
<td>Day 2 (%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>19.9</td>
</tr>
<tr>
<td>Antihistamine</td>
<td>29.4</td>
</tr>
</tbody>
</table>

- Vitamin C reduces the duration of symptoms by approximately 0.7 day when ≥1g/day is taken at onset of symptoms. Daily vitamin C during the cold season does not prevent infection.
Treatment with zinc, one lozenge every two hours while awake may reduce duration of symptoms. Nausea is a common side effect.

**Persistence of Symptoms of the Common Cold in Patients Taking Zinc Preparations**

<table>
<thead>
<tr>
<th>At 3 days</th>
<th>Zinc (%)</th>
<th>Control (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>72</td>
<td>73</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>At 5 days</th>
<th>53</th>
<th>56</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 7 days</td>
<td>31</td>
<td>46</td>
</tr>
</tbody>
</table>

**Influenza**

**Epidemiology**
- Influenza epidemics begin abruptly during the winter, reach a peak over a 2–3 week period, and last 2–3 months.
- During epidemic years, influenza causes 20,000 or more excess deaths in the United States; 90% of the deaths attributed to pneumonia and influenza occur in patients older than 65.

**Diagnosis**
- The incubation period is 18–72 hours.
- In young adults, symptoms include rapid onset of fever up to 103°F lasting 3–5 days, headache, cold symptoms, non-productive cough, myalgia, and malaise.
- Patients over 65 have lower respiratory tract symptoms (i.e. productive cough, retrosternal chest pain, or wheezing) approximately twice as often as younger patients, although rates of these findings vary in different studies.
- Elderly, debilitated patients may present with lethargy, confusion, cough, or fever and no other specific signs.
- Lab tests are usually not indicated.

**Treatment**
- Cold remedies and antipyretics for specific symptoms (as above).
- Amantadine and rimantadine are only effective against the influenza A virus. They have been shown to shorten the duration of symptoms by >1 day. Unlike patients taking amantidine for prophylaxis, patients taking these agents for treatment do not have an increased risk of CNS side effects, when compared to patients taking placebo. To be effective, antivirals must be started within 48 hours of onset of symptoms and should be continued until 48 hours after resolution.
- Zanamivir and oseltamivir (neuraminidase inhibitors) are indicated in the early treatment of influenza A and B. These agents must be given within 48 hours of the onset of symptoms.

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5. Marshall S. Zinc for the common cold. Cochrane Database of Systematic Reviews 2000;1. Because of significant side effects, variable efficacy of different formulations, and data of poor methodological quality, the authors conclude that “routine use of zinc...to treat cold symptoms is not supported”.


purulent bronchitis, otitis media, and other infections requiring antibacterial antibiotics.\(^8\,9\)

—Side effects: zanamivir is an inhaled powder which must be used with caution in patients with bronchospasm. Oseltamivir may cause nausea, vomiting, or headache.

**Prevention**

*Influenza vaccine (October through February)*

- An inactivated, egg grown vaccine containing two influenza A subtypes and one influenza B subtype, representing influenza viruses recently circulating in the world and likely to occur in the US the following winter. The vaccine is updated annually.

- **Target groups for vaccination.**\(^6\)
  - Persons 50 and older
  - Residents of long term care facilities
  - Patients with cardiopulmonary disease (asthma, CHF)
  - Patients with metabolic disease (diabetes, hemoglobinopathy, renal dysfunction, etc.)
  - Women who will be in the 2nd or 3rd trimester of pregnancy during the influenza season (December–March)
  - Household members of persons in the above groups
  - Healthcare workers
  - Healthy individuals requesting the vaccine
  - HIV positive patients

- **Contraindications:** egg allergy, acute febrile illness

- **Side effects:** soreness for 1–2 days at the injection site is the most common. Fever, malaise, and myalgias occur rarely.\(^10\)

- **Dose:** 0.5 cc IM every year

**Rates of Outcomes of Influenza Vaccination/100 Patients (aged 18–64)**\(^11\)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episodes of URI</td>
<td>140</td>
<td>105</td>
</tr>
<tr>
<td>Days of URI</td>
<td>974</td>
<td>780</td>
</tr>
<tr>
<td>Days of sick leave due to URI</td>
<td>122</td>
<td>70</td>
</tr>
</tbody>
</table>

**Influenza Vaccination and Hospitalizations/1000 patients 64 Years or Older, According to Cause**\(^12\)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>vaccine</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>8.9</td>
<td>8.4</td>
<td>5.3</td>
</tr>
<tr>
<td>Pneumonia and influenza*</td>
<td>15.6</td>
<td>24.3</td>
<td>23.7</td>
</tr>
<tr>
<td>All other resp. causes*</td>
<td>2.5</td>
<td>5.8</td>
<td>5.4</td>
</tr>
<tr>
<td>Heart failure</td>
<td>8.9</td>
<td>8.4</td>
<td>5.3</td>
</tr>
<tr>
<td>Pneumonia and influenza*</td>
<td>15.6</td>
<td>24.3</td>
<td>23.7</td>
</tr>
<tr>
<td>All other resp. causes*</td>
<td>2.5</td>
<td>5.8</td>
<td>5.4</td>
</tr>
<tr>
<td>Arm soreness*</td>
<td>20.1</td>
<td>4.9</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>5.7</td>
<td>4.2</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>8.0</td>
<td>7.7</td>
<td></td>
</tr>
<tr>
<td>Coryza</td>
<td>13.2</td>
<td>10.2</td>
<td></td>
</tr>
<tr>
<td>Myalgias</td>
<td>4.8</td>
<td>4.2</td>
<td></td>
</tr>
<tr>
<td>Headaches</td>
<td>6.9</td>
<td>7.6</td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.01

- Amantadine or rimantadine are indicated for prevention in high risk patients during the two weeks between vaccination and development of protective antibodies. When used for prophylaxis, amantadine has a higher incidence of CNS side effects than placebo. Because of this, rimantadine may be the preferred choice.\(^7\)


**Acute bacterial sinusitis**

**Epidemiology**

Approximately 0.5–2% of adults with a viral URI have a secondary bacterial infection of the paranasal sinuses.

**Diagnosis**

- Sinusitis occurs when rhinitis, polyps, foreign bodies, septal deviation, or immunodeficiency interfere with normal sinus drainage.
- It most often results from a common cold (viral rhinosinusitis).
- The diagnosis is generally made based upon the patient’s history and clinical findings; particularly those of a patient with a viral URI who is no better after 10 days or worsens after 5–7 days and has the typical findings.

**History and physical exam**

- Frequent symptoms and signs include:
  - purulent nasal discharge
  - nasal congestion
  - cough with postnasal drip
  - preceding history of URI
  - poor response to decongestants
  - hyposmia
  - pain when chewing
  - maxillary toothache
  - facial pain when leaning forward

**Likelihood Ratios for Specific Symptoms and Signs in Bacterial Rhinosinusitis**

<table>
<thead>
<tr>
<th>LR +</th>
<th>LR −</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maxillary toothache</td>
<td>2.5</td>
</tr>
<tr>
<td>Poor response to decongestants</td>
<td>2.1</td>
</tr>
<tr>
<td>Colored discharge</td>
<td>1.5</td>
</tr>
<tr>
<td>Purulent secretion</td>
<td>2.1</td>
</tr>
<tr>
<td>Abnormal transillumination</td>
<td>1.6</td>
</tr>
<tr>
<td>0 signs present</td>
<td>0.1</td>
</tr>
<tr>
<td>1 sign present</td>
<td>0.5</td>
</tr>
<tr>
<td>2 signs present</td>
<td>1.1</td>
</tr>
<tr>
<td>3 signs present</td>
<td>2.6</td>
</tr>
<tr>
<td>4 or 5 signs present</td>
<td>6.4</td>
</tr>
</tbody>
</table>

- **Transillumination** should be performed in a dark room.
  - For frontal sinusitis: direct the light superiorly, from below the supraorbital rim, and observe for transmission through the forehead.
  - For maxillary sinusitis: direct the light inferiorly through the infraorbital rim and look for transillumination through the hard palate.
  - Opacity suggests infection.

---

Influenza Rates with Amantadine/Rimantadine Prophylaxis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Control</th>
<th>ARR*</th>
<th>RRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amantadine</td>
<td>Placebo</td>
<td>15%</td>
<td>63%</td>
</tr>
<tr>
<td>Rimantadine</td>
<td>Placebo</td>
<td>8%</td>
<td>73%</td>
</tr>
</tbody>
</table>

*Weighted ARR calculated by this author

The frontal, maxillary, ethmoid, and sphenoid sinuses produce up to a liter of mucus a day.

---


14 Williams JW, Simel DL. Does this patient have sinusitis? Diagnosing acute sinusitis by history and physical exam. JAMA 1993;270:1242–6.
Diagnostic tests
- In most cases, only history and physical exam are needed to make the diagnosis.
- Further testing is indicated if symptoms do not resolve or if they recur quickly after treatment.

Sinus radiographs
- Most useful in those who fail to respond to initial treatment.
- About 85% of patients with sinusitis have maxillary sinusitis.\(^\text{15}\)
- A standard four-view series is most accurate in patients with maxillary sinusitis.\(^\text{14}\) A single Waters’ view is highly concordant with a four-view series, though less so for frontal and ethmoid sinuses.\(^\text{15}\)
- Radiographic findings in acute sinusitis include opacification, air–fluid levels, and mucosal thickening.
- The chief limitations of these studies are poor visualization of the ethmoid air cells and difficulty distinguishing between infection, tumor, and polyp in the presence of opacification.

Accuracy of Sinus Radiograph Findings in Acute Sinusitis\(^\text{16}\)

<table>
<thead>
<tr>
<th></th>
<th>Sens (95% CI)</th>
<th>Spec (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus opacity</td>
<td>41%</td>
<td>85%</td>
</tr>
<tr>
<td>Sinus fluid or opacity</td>
<td>73%</td>
<td>80%</td>
</tr>
<tr>
<td>Sinus fluid or opacity or mucous membrane thickening</td>
<td>90%</td>
<td>61%</td>
</tr>
</tbody>
</table>

CT and MRI
- CT is extremely sensitive but lacks specificity. Eighty-seven percent of patients with a cold have CT abnormalities.
- Indications for CT include:
  - recurrent episodes of clinical sinusitis with negative radiographs
  - evaluation of local extension of infection
  - preoperative evaluation.
- MRI is useful for distinguishing malignancy from infection.

Indications for referral to ENT
- Treatment failure after two courses of antibiotics
- Deterioration of symptoms within two days
- Complications
- Severe pain due to complete osteal obstruction
- Frequent recurrences (> 3 episodes/year)
- Immunocompromise
- Unclear diagnosis

Treatment
- Treatment goals
  - Symptomatic relief
  - Avoidance of the complications of direct extension of infection: orbital cellulitis, brain abscess, meningitis, osteomyelitis, and cavernous sinus thrombosis.

Aspiration of the sinus is the diagnostic gold standard. Only the maxillary sinus can be aspirated percutaneously.

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\(^\text{15}\) Agreement Between Waters’ View and Complete Four-View Radiography Series in Sinusitis

<table>
<thead>
<tr>
<th></th>
<th>Residents</th>
<th>Attendings</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sinuses</td>
<td>84</td>
<td>75</td>
</tr>
<tr>
<td>SA(%)</td>
<td>0.68</td>
<td>0.50</td>
</tr>
<tr>
<td>Maxillary</td>
<td>94</td>
<td>86</td>
</tr>
<tr>
<td>SA(%)</td>
<td>0.87</td>
<td>0.72</td>
</tr>
<tr>
<td>Frontal</td>
<td>83</td>
<td>75</td>
</tr>
<tr>
<td>SA(%)</td>
<td>0.21</td>
<td>0.08</td>
</tr>
<tr>
<td>Ethmoid</td>
<td>77</td>
<td>84</td>
</tr>
<tr>
<td>SA(%)</td>
<td>0.16</td>
<td>0.02</td>
</tr>
<tr>
<td>Sphenoid</td>
<td>93</td>
<td>91</td>
</tr>
<tr>
<td>SA(%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Engels EA, Terrin N, Barza M, Lau J. Meta-analysis of diagnostic tests for acute sinusitis. J Clin Epidemiol 2000;53:852–62. Analysis of data from 495 patients in six trials comparing 2–3 radiographic views with sinus puncture. A Waters’ view was performed in each trial. Streptococcus pneumoniae and Haemophilus influenzae account for approximately 60–70% infections in bacterial rhinosinusitis. There is a reported 39% resistance of \(H.\) influenzae to amoxicillin and 6% to amoxicillin/clavulanate.
Symptomatic relief with analgesics, topical mucolytics, nasal corticosteroids, and decongestants.

Environmental humidification and adequate hydration

Treatment of the primary cause of nasal obstruction

Antibiotics for 10–14 days\textsuperscript{17,18}

—Initially: amoxicillin or amoxicillin/clavulanate; for penicillin allergic: trimethoprim/sulfamethoxazole or doxycycline.

—If symptoms worsen or do not improve within 72 hours start levofloxacin or amoxicillin/clavulanate if patient was on amoxicillin alone.

Refer to ENT if the patient fails a second course of antibiotics. Also consider immunodeficiency: HIV, diabetes, cystic fibrosis.

**Group A β hemolytic streptococcus pharyngitis**

The diagnostic task is to distinguish infection with group A Streptococcus from chronic tonsillitis and infection with *Neisseria gonorrhoeae*, *Candida albicans*, or Epstein-Barr virus (mononucleosis).

It is important to diagnose infection with group A streptococcus given the potential for rheumatic fever and suppurative complications.

It has not been established that treatment of pharyngitis caused by other organisms benefits the patient.

**Diagnosis**

**Clinical presentation**\textsuperscript{19}

- Acute onset of sore throat
- Most commonly occurs in autumn

**Physical exam score**\textsuperscript{20}

- Assign one point for each of the following findings:
  - fever or history of fever
  - tonsillar exudates
  - anterior cervical adenopathy
  - absence of cough.

- Scoring
  - 0–1 Very low risk: reassurance and treatment of symptoms
  - 2–3 Moderate risk: diagnostic testing
  - 4 High risk: empiric treatment

**Diagnostic testing**

- Perform in patients with a physical exam score of 2–3.
- It should include a rapid antigen test (“rapid strep test”) to be followed by throat culture if negative.\textsuperscript{21}
- If a rapid test is not available, proceed with a throat culture.\textsuperscript{20}

**Treatment**

Antibiotic treatment is indicated for patients with a positive diagnostic test, a physical exam score of 4, or for patients with a score of 2–3 where there is no rapid test who are awaiting the results of the throat culture.

---

\textsuperscript{17} De Ferranti SD, Ioannidis JPA, Lau J, Anninger WV, Barza M. Are amoxicillin and folate inhibitors as effective as other antibiotics for acute sinusitis? A meta-analysis. BMJ 1998; 317:632–7. 2717 patients with acute sinusitis or exacerbations of chronic sinusitis in 27 trials. To calculate ARR from data below, note that 31%,11%, and 11% of patients on placebo, amoxicillin, and folate inhibitors had clinical failure.

**Sinusitis: Old v New Antibiotics**

<table>
<thead>
<tr>
<th>RR of treatment</th>
<th>Treatment</th>
<th>Control</th>
<th>failure (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Abx.</td>
<td>Placebo</td>
<td>0.54</td>
<td>0.37–0.79</td>
</tr>
<tr>
<td>New Abx.</td>
<td>Amox</td>
<td>0.86</td>
<td>0.62–1.19</td>
</tr>
<tr>
<td>New Abx.</td>
<td>Folate</td>
<td>1.01</td>
<td>0.52–1.97</td>
</tr>
</tbody>
</table>

Abx = antibiotics

Amox = amoxicillin


**Etiologies of Pharyngitis**

<table>
<thead>
<tr>
<th>Organism</th>
<th>Percent of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virus</td>
<td>50–80</td>
</tr>
<tr>
<td>Streptococcus</td>
<td>5–36</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>1–10</td>
</tr>
<tr>
<td><em>Chlamydia pneumoniae</em></td>
<td>2–5</td>
</tr>
<tr>
<td><em>Mycoplasma pneumoniae</em></td>
<td>2–5</td>
</tr>
<tr>
<td><em>Neisseria gonorrhoeae</em></td>
<td>1–2</td>
</tr>
<tr>
<td><em>Haemophilus influenza b</em></td>
<td>1–2</td>
</tr>
<tr>
<td>Candida</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>


• Treatment is given primarily to prevent rheumatic fever. It does little to shorten the 3–5 day course of the disease.
• Regimens:
  —benzathine penicillin G, 1.2 million units IM × 1 dose
  —penicillin V, 250 mg PO tid or 500 mg PO bid × 10 days
  —for penicillin allergic patients: erythromycin, 250 mg PO qid × 10 days.

Chronic tonsillitis
• Chronic tonsillitis presents as recurrent sore throats, enlarged tonsils, and lymphadenopathy.
• Medical treatment consists of clindamycin 300 mg or amoxicillin/clavulanate 500 mg three times a day for seven days.
• Indication for tonsillectomy: ≥4 episodes of bacterial tonsillitis for at least two years with ≥10 missed days of school or work per year.  

Mononucleosis
• Patients with a sore throat but who are without fever, cervical adenopathy, splenomegaly, or palatal petechiae do not have Epstein-Barr mononucleosis (LR = 0).  
• The presence of any of these four signs merits a white blood cell count with differential or a rapid slide (monospot) test.
• Greater than 50% lymphocytosis (including atypical cells) or a positive monospot confirms the diagnosis (LR = 49). Both tests may be falsely negative during the first week of illness.

Allergic rhinitis
Epidemiology  
• Allergic rhinitis is the most common form of atopic disease. Prevalence varies widely in different studies, between 4% and 40%. Prevalence does not vary significantly with differences in geographic location, socioeconomic status, or sex.
• It is associated with asthma, sinusitis, otitis media with effusion, and nasal polyps.

Diagnosis
History
• Symptoms include watery rhinorrhea, sneezing, nasal congestion, postnasal drip, palatal itching, and conjunctivitis.
• Key questions
  —Are the symptoms seasonal or perennial?
  —Are there allergens at the workplace?
  —Family history of atopy? Eczema during childhood?

Physical exam
• Pale, bluish, swollen nasal mucosa (seen in 50–60% of cases)
• Nasal polyps
• Clear, thin nasal discharge
UPPER RESPIRATORY INFECTION AND ALLERGIC RHINITIS

- Erythematous throat with cobblestoning of the posterior pharynx representing lymphoid hyperplasia
- Conjunctival infection
- “Allergic shiner”: dark discoloration beneath the lower eyelid.
- “Allergic gape”: continuous open mouth breathing

TREATMENT

- Avoidance: control dust, remove pets, close windows, seal mattresses in zippered covers, use air conditioning, maintain humidity at <50% to reduce the dust mite population.
- Decongestants: oxymetazoline and pseudoephedrine
- Antihistamines (H1 blockers)
  - Reduce sneezing, rhinorrhea, pruritus, and eye symptoms
  - These are most effective when used before an anticipated allergen exposure.
  - First generation agents are inexpensive but cause more sedation than second generation agents.
- Corticosteroids are better than antihistamines for almost every measure of nasal symptomatology.25
  - The relative risk for deterioration of symptoms for patients taking intranasal corticosteroids, compared to those taking antihistamines, is 0.26 (95% CI = 0.08 to 0.8).
  - Systemic side effects are negligible.

**Benefit of Intranasal Corticosteroids v H1 Receptor Antagonists in Allergic Rhinitis**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Agent favored</th>
<th>Standardized mean difference (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal blockage</td>
<td>Corticosteroid</td>
<td>−0.63 (−0.73 to −0.53)</td>
</tr>
<tr>
<td>Nasal discharge</td>
<td>Corticosteroid</td>
<td>−0.5 (−0.6 to −0.4)</td>
</tr>
<tr>
<td>Sneezing</td>
<td>Corticosteroid</td>
<td>−0.49 (−0.59 to −0.39)</td>
</tr>
<tr>
<td>Postnasal drip</td>
<td>Corticosteroid</td>
<td>−0.24 (−0.42 to −0.06)</td>
</tr>
<tr>
<td>Total nasal score</td>
<td>Corticosteroid</td>
<td>−0.42 (−0.53 to −0.32)</td>
</tr>
<tr>
<td>Ocular symptoms</td>
<td>Both equivalent</td>
<td>−0.04 (−0.16 to 0.07)</td>
</tr>
</tbody>
</table>

- Cromolyn sodium is effective for nasal symptoms. Start 3–7 days before the allergy season begins, and continue throughout.
- Naphazoline ophthalmic solution is a topical antihistamine useful for associated ophthalmologic symptoms.
- In allergen immunotherapy, increasing amounts of allergen extracts are injected subcutaneously over a varying time span to decrease the symptoms that arise upon exposure.26
  - It is useful in seasonal allergic rhinitis (hayfever). Its use is limited in perennial rhinitis because patients have sensitivity to many allergens.
- Treatment of nasal symptoms during pregnancy27
  - Best treatment: allergen avoidance, nasal saline
  - Category B medications include chlorpheniramine, loratidine, cetirizine, pseudoephedrine, and cromolyn.


Referral
- If the patient fails to respond to conservative treatment, referral to an allergist for further diagnosis (prick testing or RAST) and more aggressive therapy (oral steroids, immunotherapy) is appropriate.

Radioallergosorbent technique (RAST)
Measurement of specific anti-IgE in serum by its binding to a solid phase allergen and quantification by the subsequent uptake of radiolabeled anti-IgE.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Dosage</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antivirals</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amantadine (Symmetrel)</td>
<td>100 mg tablet</td>
<td>100 mg PO bid</td>
<td>Same dosage for treatment and prophylaxis. Use ≤100 mg/day for patients over 65. Dose adjust for GFR ≤50 ml/min. May cause GI or CNS side effects.</td>
</tr>
<tr>
<td></td>
<td>100 mg/10 cc syrup</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rimantadine (Flumadine)</td>
<td>100 mg tablets</td>
<td>100 mg PO bid</td>
<td>100 mg/day for elderly nursing home patients, patients with GFR ≤ 10 ml/min, or severe hepatic dysfunction. Same dosage for treatment and prophylaxis. May cause GI or CNS side effects, but fewer than amantadine.</td>
</tr>
<tr>
<td></td>
<td>100 mg/10 cc syrup</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zanamivir (Relenza)</td>
<td>5 mg/blister</td>
<td>2 puffs bid</td>
<td>Patients need instruction on use of the diskhaler inhalation device. May cause bronchospasm in patients with asthma or COPD. These patients should take zanamivir after the scheduled bronchodilator dose.</td>
</tr>
<tr>
<td>Oseltamivir (Tamiflu)</td>
<td>75 mg</td>
<td>75 mg PO bid</td>
<td>Dose adjust for GFR ≤30 ml/min. May cause nausea and vomiting.</td>
</tr>
<tr>
<td><strong>First generation antihistamines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphenhydramine (Benadryl)</td>
<td>25 mg</td>
<td>25 mg PO q6 prn</td>
<td>Prominent anticholinergic side effects, contraindicated in BPH, narrow angle glaucoma.</td>
</tr>
<tr>
<td>Doxylamine (Unisom)</td>
<td>25 mg (scored)</td>
<td>12.5 mg PO q6 prn</td>
<td></td>
</tr>
<tr>
<td>Chlorpheniramine (Chlor-Trimeton)</td>
<td>4 mg</td>
<td>4 mg PO q6 prn</td>
<td>Less sedating than doxylamine or diphenhydramine</td>
</tr>
<tr>
<td><strong>Second generation antihistamines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Astemizole (Hismanal)</td>
<td>10 mg</td>
<td>10 mg PO qd</td>
<td>Avoid in patients with hepatic dysfunction. Do not use with clarithromycin, erythromycin, itraconazole, or quinine; these raise drug levels and may cause prolonged QT or torsades de pointes.</td>
</tr>
<tr>
<td>Drug</td>
<td>Formulation</td>
<td>Dosage</td>
<td>Comments</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Loratadine (Claritin)</td>
<td>10 mg tablets</td>
<td>10 mg PO qd</td>
<td>Start at 1 tablet qod or 5 cc syrup qd in patients with GFR &lt; 30 ml/min or hepatic dysfunction.</td>
</tr>
<tr>
<td></td>
<td>1 mg/ml syrup</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fexofenadine (Allegra)</td>
<td>60 mg</td>
<td>60 mg PO bid</td>
<td>Start at 60 mg qd in patients over 65 or patients with GFR &lt; 80 ml/min.</td>
</tr>
<tr>
<td>Cetirizine (Zyrtec)</td>
<td>5 mg, 10 mg</td>
<td>5–10 mg PO qd</td>
<td>No anticholinergic side effects. Start at 5 mg/day in patients with GFR &lt; 30 cc/min or patients with impaired hepatic function.</td>
</tr>
<tr>
<td>Decongestants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudoephedrine (Sudafed)</td>
<td>30 mg, 60 mg</td>
<td>30–60 mg PO q4–6 prn</td>
<td></td>
</tr>
<tr>
<td>(Sudafed SR)</td>
<td>120 mg</td>
<td>120 mg PO q12</td>
<td></td>
</tr>
<tr>
<td>Oxymetazoline (Afrin,</td>
<td>0.05%</td>
<td>2–3 sprays each nostril bid (for ≤ 4 days)</td>
<td></td>
</tr>
<tr>
<td>Neosynephrine)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical nasal corticosteroids</td>
<td>55 micrograms/puff</td>
<td>2 puffs each nostril</td>
<td>Most effective if begun before exposure to allergens. May take up to two weeks to have effect. Use AQ formula for dry or irritated nose. May cause nasal irritation, epistaxis or headaches. May reduce to 1 puff qd after control.</td>
</tr>
<tr>
<td>Triamcinolone (Nasacort)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beclomethasone (Vancenase)</td>
<td>42 micrograms/puff</td>
<td>2 sprays each nostril bid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>84 micrograms/puff</td>
<td>1–2 sprays each nostril bid</td>
<td></td>
</tr>
<tr>
<td>Mucolytics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guaifenesin (Humibid L.A.)</td>
<td>600 mg</td>
<td>600–1200 mg bid</td>
<td></td>
</tr>
<tr>
<td>Saline nasal spray</td>
<td></td>
<td>2 sprays/b nostril prn</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naphazoline ophthamlic</td>
<td></td>
<td></td>
<td>Avoid in patients with narrow angle glaucoma</td>
</tr>
<tr>
<td>solution (Naphcon)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cromolyn sodium nasal</td>
<td>5.2 mg/spray</td>
<td>1 spray each nostril</td>
<td>May take up to 1 week to show effect. If needed, may increase to 6 times per day</td>
</tr>
<tr>
<td>solution (Nasalcrom)</td>
<td></td>
<td>3–4 times per day</td>
<td></td>
</tr>
<tr>
<td>Ipratropium bromide</td>
<td>0.03%,</td>
<td>2 sprays qid prn</td>
<td>Reduces rhinorrhea from any cause; not very effective for other nasal symptoms. May use with nasal corticosteroids.</td>
</tr>
<tr>
<td>(Atrovent) nasal spray</td>
<td>0.06%</td>
<td>2 sprays qid prn</td>
<td></td>
</tr>
</tbody>
</table>
40 Valvular heart disease

Roxana Lascu

Aortic stenosis

Epidemiology

- Aortic stenosis is caused by degeneration and calcification of valve leaflets. It usually develops in patients over the age of 60.
- Earlier development may occur with a history of congenital bicuspid valve. Calcification of a bicuspid leaflet can lead to significant stenosis as early as 40 years of age.

Diagnosis

Symptoms and prognosis

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Mean survival without valve replacement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>Normal life expectancy</td>
</tr>
<tr>
<td>Angina</td>
<td>5 years</td>
</tr>
<tr>
<td>Exertional syncope</td>
<td>3 years</td>
</tr>
<tr>
<td>Heart failure (systolic or diastolic)</td>
<td>2 years</td>
</tr>
</tbody>
</table>

Physical exam

- The carotid upstroke is diminished or delayed (pulsus parvus et tardus).
- A late peaking systolic ejection murmur is heard at the base and may radiate to the neck.
- The aortic component of the second heart sound is diminished.
- The murmur may decrease in intensity as the stenosis worsens and the left ventricle fails.
- A thrill may be palpable in the suprasternal notch.

Diagnosis and severity assessment

- Electrocardiogram (ECG) may show left ventricular hypertrophy.
- Chest radiograph may show left ventricular enlargement.
- Echocardiography with Doppler helps to assess valve area. The normal valve area is $\sim 2.5 \text{ cm}^2 (1.5 \text{ cm}^2/\text{m}^2$ body surface area). Aortic stenosis is usually clinically evident by the time the valve area is $< 1/3$ normal.
- Critical aortic stenosis is associated with a transvalvular pressure gradient of $> 50 \text{ mmHg}$. This corresponds to an aortic jet velocity of $\sim 3.5 \text{ m/s}$.
- Invasive tests are not usually needed to determine severity; however, coronary angiography is indicated in the setting of angina or heart failure to evaluate for coronary artery disease.

Treatment

- The prognosis of aortic stenosis is dependent upon the presence of symptoms. In the absence of symptoms, life expectancy is similar to age matched controls. As soon as symptoms develop, however, survival drops precipitously.  


An audibly split second heart sound is evidence against severe aortic stenosis.
The majority of symptomatic patients with aortic stenosis will die within three years if untreated.\(^2\)

- Surgical therapy with valve replacement is the only treatment for aortic stenosis that has shown survival benefit.\(^3\) Since clinical symptoms are the best predictor of mortality, it is the development of symptoms that dictates the timing of surgery.
- Many researchers have attempted to identify subsets of asymptomatic patients with particularly poor prognoses who might benefit from surgery prior to the onset of symptoms. The degree of valve calcification may be one such predictor.\(^4\)
- Even patients with advanced symptoms can experience significant improvement in contractile function and symptoms,\(^5\) though there is increased surgical risk in this group.
- Age is not a contraindication to surgery.
- Balloon valvuloplasty may be considered for patients who cannot tolerate surgery but there is a high complication rate and poor overall survival.\(^6\) This technique is rarely used.
- Asymptomatic patients can safely be followed clinically until the development of symptoms. Because most of these patients are elderly, care must be taken to tease out the often subtle, slowly progressing symptoms of decreased exercise tolerance, fatigue, and malaise that might otherwise be attributed to aging.
- All patients with aortic stenosis should receive prophylaxis for bacterial endocarditis (see section below on Endocarditis, Prophylaxis).

### Mitral stenosis

**Epidemiology**

- Mitral stenosis is almost always a consequence of rheumatic heart disease.
- The incidence of mitral stenosis is declining in developed countries, in parallel with the decline in rheumatic heart disease. This is not the case in developing countries.

**Diagnosis**

**Symptoms**

- Dyspnea on exertion and paroxysmal nocturnal dyspnea are secondary to decreased left ventricular filling.
- Increased left atrial size may lead to atrial fibrillation and palpitations.
- Increased resistance at the mitral valve leads over time to pulmonary hypertension and symptoms of right ventricular failure.

**Physical exam**

- The murmur of mitral stenosis is described as a diastolic rumble that follows an opening snap. It is enhanced by squatting.

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\(^3\) Schwartz F, Baumann P, Manthey J et al. The effect of aortic valve replacement on survival. Circulation 1982;66: 1105–10. In a retrospective analysis of 299 patients with aortic stenosis for whom valve replacement had been recommended, survival at three years was 87% in the 252 patients who had surgery and 21% in the 47 who declined surgery.

\(^4\) Rosenhek R, Binder T, Porenta G et al. Predictors of outcome in severe, asymptomatic aortic stenosis. N Engl J Med 2000;343:611–7. 128 patients with severe but asymptomatic aortic stenosis were followed prospectively for an average of 22 months. Eight died and 59 developed symptoms requiring valve replacement. The extent of aortic valve calcification, but not age, sex, coronary artery disease, hypertension, diabetes or cholesterol, was a predictor of outcome.


\(^6\) Otto CM, Mickel MC, Kennedy JW et al. Three-year outcome after balloon aortic valvuloplasty: insights into prognosis of valvular aortic stenosis. Circulation 1994;89:642–50. In this prospective evaluation of 674 patients after valvuloplasty, one and three year survival rates were 55% and 23%, respectively.
• A loud S1 is due to the leaflets being kept open longer than normal by high left atrial pressure, until they are forced shut by systole.
• Right ventricular failure is suggested by jugular venous distension, loud pulmonary component of the second heart sound, and ascites or edema.

**Diagnosis and severity assessment**
• Chest radiograph characteristically shows a double contour of the right heart shadow consistent with left atrial enlargement, as well as a straightening of the left heart border and a splayed carina (>90° angle).
• The electrocardiogram may show left atrial enlargement.
• Echocardiography is the least invasive and most accurate tool for determining presence and degree of stenosis.\(^7\)
• Valve area is estimated by measuring the flow velocity and calculating transvalvular gradient.\(^8\)

**Treatment**
• Treatment for mitral stenosis is determined by the presence of symptoms and atrial fibrillation.
• For patients without symptoms and in sinus rhythm, no treatment is needed, other than clinical follow up.
• For patients with mild symptoms, in the absence of atrial fibrillation, diuretics and β blockers have been suggested, but there is little evidence to support this.\(^9\)

**Atrial fibrillation**
• Rate control with β blockers, calcium channel blockers or digoxin is uniformly recommended to allow adequate filling time, but this has never been studied in a prospective manner.
• The risk of stroke in valvular atrial fibrillation is not precisely known, but it is estimated to be 5–8% per year.\(^10\)
• Unlike the much larger population of patients with non-valvular atrial fibrillation, the effect of anticoagulation in valvular atrial fibrillation has never been studied in a prospective, randomized manner. Patients with valvular atrial fibrillation have routinely been excluded from the large trials of anticoagulation.
• The beneficial effects of anticoagulation on stroke reduction seen in non-valvular atrial fibrillation\(^11\) are the only data upon which to base treatment decisions. The results are presumed to be similar for those with valvular atrial fibrillation, but this has not been clearly determined.
• All patients with valvular atrial fibrillation should be anticoagulated with warfarin, with a target INR of 2.0–3.0.

**Surgery**
• For patients with moderate to severe symptoms or evidence of severe pulmonary hypertension (>75 mmHg), mechanical correction of the obstruction is necessary.\(^12\)
Options include balloon valvuloplasty, surgical commissurotomy, valve repair and valve replacement. There are few head to head trials comparing these procedures. Balloon valvuloplasty appears to be less effective when the valve is severely deformed. All patients with mitral stenosis should receive prophylaxis for bacterial endocarditis (see section below on Endocarditis, Prophylaxis).

Mitral regurgitation

Epidemiology

The major causes of mitral regurgitation are:
- Rheumatic heart disease
- Myxomatous degeneration and calcification of the mitral valve
- Ischemia or infarction leading to fibrosis of a papillary muscle
- Mitral valve prolapse
- Endocarditis

Trace mitral regurgitation is extremely common. Its significance has never been prospectively evaluated, but it is generally considered to be benign.

Diagnosis

Physical exam
- Holosystolic apical murmur.
- S3 caused by rapid filling of the left ventricle.
- The murmur of mitral regurgitation is enhanced by maneuvers that increase peripheral impedance, such as squatting.
- Signs of left atrial enlargement (from chronic fluid overload) may be seen on chest radiograph and ECG.
- A displaced point of maximal impulse may be a sign of left ventricular dilatation caused by volume overload.

Diagnosis and severity assessment
- Unlike mitral stenosis or aortic stenosis, mitral regurgitation symptoms are not an accurate predictor of outcome.
- Because of the regurgitation, ejection fraction may actually be supranormal. A decline of ejection fraction to less than 60% is associated with worse outcomes.
- Left ventricular dilatation, with endsystolic diameters of more than 45–50 mm, also predict poor prognosis.
- Echocardiography and ventriculography can assess ejection fractions and ventricular dimension.

Treatment
- Unlike mitral and aortic stenosis, the decision to intervene surgically for mitral regurgitation is not necessarily based on symptoms. When the left ventricle is no longer hyperdynamic or when the endsystolic dimension reaches 4.5 cm surgery should be contemplated even in asymptomatic patients.

13 Reyes VP, Raju BS, Wynne J et al. Percutaneous balloon valvuloplasty compared with open surgical commissurotomy for mitral stenosis. N Engl J Med 1994;331:961–7. 60 patients with severe mitral stenosis were randomized to balloon valvuloplasty or surgical commissurotomy. More patients in the valvuloplasty group (72% v 57%) were symptom free at three years. Valvuloplasty achieved a larger valve area, but there were more ASDs. Restenosis rates were similar (10%).


15 Singh JP, Evans JC, Levy D et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). Am J Cardiol 1999;83:897–902. More than 2000 subjects in the Framingham cohort were given echocardiograms during routine visits. Prevalence of trace mitral regurgitation was seen in up to 75% of subjects, but moderate to severe regurgitation was seen in 1–2.5% of subjects ≥50 years and in less than 1% of younger subjects.

- 100% for EF > 60%
- 72% for EF 50–60%
- 32% for EF < 50%.

Valve repair and valve replacement have never been directly compared in a prospective, randomized trial, but repair has the advantage of not requiring anticoagulation and involves less surgical risk. Most experts recommend repair over replacement if surgically feasible.

Medical therapy with afterload reduction is theoretically beneficial, but this has not been borne out in the few small trials that have studied this.\(^\text{18}\)

All patients with mitral regurgitation should receive prophylaxis for bacterial endocarditis (see section below on Endocarditis, Prophylaxis).

### Mitral valve prolapse

**Epidemiology**
- In the past, the quoted incidence has been 5–15%.
- A recent assessment of community based prevalence found mitral valve prolapse in only 2.4% of the population.\(^\text{19}\)
- The higher previous estimates are thought to be due to referral bias and non-uniform echocardiographic diagnostic criteria.
- The most feared sequelae historically associated with mitral valve prolapse (atrial fibrillation, syncope, heart failure, and cerebrovascular disease) appear to be much rarer than previously thought. They do not seem to be any more prevalent than in patients without mitral valve prolapse.\(^\text{19,20}\)
- The underlying pathology often involves myxomatous degeneration of the valves and/or redundant mitral valve leaflets.
- Connective tissue disorders such as Marfan syndrome or Ehlers–Danlos syndrome are predisposing conditions.

**Diagnosis**

**Symptoms**
- Atypical chest pain, dizziness, and palpitations have been reported, though in the Framingham analysis they were no more common than controls.\(^\text{19}\)
- The vast majority of patients with mitral valve prolapse are asymptomatic and are identified during routine physical exam.

**Physical exam**
- A mid to late systolic click is caused by the prolapsing mitral leaflets. It may be followed by a regurgitant murmur.
- Mitral valve prolapse is also referred to as the “click-murmur syndrome”.

**Diagnosis and severity assessment**
- Echocardiography is the best non-invasive method to evaluate the mitral valve. Criteria have varied in different studies, but ones used in the two cited studies\(^\text{19,20}\) and that appear to be gathering consensus can be summarized as:
  - redundant and thickened leaflets constitute mitral valve prolapse

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**Appetite suppressants and valvular heart disease**

In 1997, the FDA withdrew fenfluramine and phentermine after cases of aortic and mitral regurgitation were reported. Structurally, the lesions resembled the serotonin related changes seen in carcinoid syndrome. Subsequent studies varied in methodology and populations, but there appeared to be an association with duration of use, with little risk for short term (<4 months) use. Obesity alone did not appear to be a risk factor for valvular disease. Data summary: Devereux RB. Appetite suppressants and valvular heart disease. N Engl J Med 1998;339:765–6.

\(^\text{19}\) Freed LA, Levy D, Levine RA et al. Prevalence and clinical outcome of mitral valve prolapse. N Engl J Med 1999;341:1–7. This study from the Framingham offspring cohort confirmed a slightly higher prevalence in women than men: 2.7% v 2.1%. The prevalence of chest pain, dyspnea and ECG abnormalities was no different than control. The prevalence of adverse outcomes v controls was:
- Syncope 3.6% v 3.0%
- Atrial fibrillation 1.2% v 1.7%
- Cerebrovascular disease 1.2% v 1.5%
- Heart failure 0% v 0.7%.

\(^\text{20}\) Gilon D, Buonanno FS, Joffé MM et al. Lack of evidence of an association between mitral-valve prolapse and stroke in young patients. N Engl J Med 1999;341:18–13. In this case control analyses of 213 patients <45 years old with stroke or TIA, the frequency of mitral valve prolapse was 1.9%, compared with 2.7% in matched controls.
—presence or absence of regurgitant flow should be noted
—mild bowing with normal appearing leaflets is considered a normal variant.

- Patients with a mid-systolic click or characteristic murmur should be evaluated by echocardiogram.
- Echocardiography is probably of low yield in patients with symptoms of chest pain, dyspnea, or palpitations in the absence of a click or murmur.

**Treatment**
- There is no treatment for mitral valve prolapse, *per se*, other than reassurance.
- If there is associated mitral regurgitation, patients should be evaluated and treated for the regurgitation.
- For patients with thickened leaflets, close clinical follow up is warranted to evaluate for the development of regurgitation. There are no data to describe how frequently echocardiograms should be done.
- Antibiotics for endocarditis prophylaxis are recommended if there are thickened or calcified leaflets, or mitral regurgitation.

### Aortic regurgitation

**Epidemiology**
The major causes of aortic regurgitation are:
- damaged valve leaflets from rheumatic heart disease
- aortic root dilatation secondary to:
  - syphilis
  - collagen vascular disease
  - Marfan syndrome
  - aortic dissection
  - unknown causes.
- The prevalence of aortic regurgitation increases with age.\(^{21}\)

**Diagnosis**

**Symptoms**
- Exertional dyspnea and fatigue are the most common symptoms.
- Paroxysmal nocturnal dyspnea
- Typical or atypical chest pain

**Physical exam**
- Diastolic blowing murmur at the left sternal border\(^{22}\)
- Systolic hypertension
- Wide pulse pressure which need not correspond to severity of aortic insufficiency.
- A prominent apical impulse which may also be hyperdynamic
- Symptoms consistent with left sided heart failure. These usually occur late in the disease.

**Diagnosis and severity assessment**
- Echocardiography with Doppler can determine amount of regurgitant flow, left ventricle dimensions, and ejection fraction.

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**Austin Flint murmur:** diastolic rumble heard over the cardiac apex; produced by the regurgitant jet striking the anterior leaflet of the mitral valve, obstructing mitral flow.

Dr Austin Flint was a professor of medicine at the Bellevue Hospital Medical College for 25 years (1861–86). During that time he brought the binaural stethoscope into general use in the US and wrote his *Treatise on the Principles and Practice of Medicine* (1866).

\(^{21}\) Singh JP, Evans JC, Levy D et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). *Am J Cardiol* 1999;83:897–902. More than 2000 subjects in the Framingham cohort were given echocardiograms during routine visits. Prevalence of any aortic regurgitation was 13.0% in men and 8.5% of women, and increased with age. Moderate or severe aortic regurgitation was seen in 2% of patients ≥70 years and less than 1% in younger patients.

\(^{22}\) Choudhry NK, Etchells EE. Does this patient have aortic regurgitation? *JAMA* 1999;281:2231–8. The presence of a typical aortic regurgitation murmur increased the likelihood of aortic regurgitation (LR range 4–32), but most studies in this review examined the clinical skills of cardiologists only.
fraction. Endsystolic diameter > 55 mm and ejection fraction < 55% are both poor prognostic indicators (“rule of 55”).23
• Presence of symptoms is also associated with poor prognosis, because it usually indicates impaired ventricular function.24

Treatment
• The increased afterload seen in aortic regurgitation can be mitigated somewhat with vasodilators. This can improve left ventricular hemodynamics25 and may temporarily postpone the need for surgery.26
• Both calcium channel blockers and ACE inhibitors have shown salutary effects and, based on a single, head to head trial, ACE inhibitors may be more efficacious.27
• The goal of surgical intervention is to replace the valve before permanent ventricular damage occurs. Usually progressive ventricular dysfunction is accompanied by symptoms, but in the case of advanced hemodynamic compromise in asymptomatic patients, surgery is recommended (“rule of 55”, see above).23

Bacterial endocarditis
Prophylaxis
Overview
• No prospective study has been done to date to prove that this common practice is effective.
• Pre-existing cardiac abnormalities and a prior history of endocarditis place patients at a higher risk for subsequent endocarditis,28 but it is unclear if elective procedures are actually responsible for the endocarditis.29
• There are very few data about the actual incidence of endocarditis30 in the various populations, and even less in relation to elective procedures.29
• The American Heart Association guidelines31 emphasize the need for case by case evaluation.

Factors affecting decision to institute prophylaxis
• The risk of endocarditis posed by the underlying cardiac condition
• The risk of bacteremia with the procedure
• The potential adverse effects of the antimicrobial regimen
• The cost–benefit ratio32
• Endocarditis prophylaxis is currently recommended in cardiac conditions associated with moderate and high risk for endocarditis (see Box 40.1).

Procedures for which prophylaxis is recommended31
• Dental procedures
  —Extractions
  —Periodontal procedures (surgery, scaling, root planing, probing, recall maintenance)
  —Implants
  —Root canal

26 Scognamiglio R, Rahimtoola SH, Fosoli G et al. Nifedipine in asymptomatic patients with severe aortic regurgitation and normal left ventricular function. N Engl J Med 1994;331:689–94. 143 patients with severe, asymptomatic aortic regurgitation were randomized to nifedipine or digoxin. At six years, valve replacement had been done in 15% and 34% of the two groups, respectively.
29 Strom B, Altmyn E, Berlin JA et al. Dental and cardiac risk factors for infective endocarditis. A population-based, case-control study. Ann Intern Med 1998;129:761–9. This case control study compared 273 patients with endocarditis not associated with IV drug use. Compared to matched controls, they were no more likely to have had dental procedures in the preceding three months. Adjusted odds ratios for various conditions (determined by selfreport and by medical records):
• Any valve disease OR = 131
• Previous valve surgery OR = 75
• Previous endocarditis OR = 37
• Mitral valve prolapse OR = 19
• Rheumatic fever OR = 13
• Congenital heart disease OR = 7
• Heart murmur OR = 4
—Initial placement of orthodontic bands (but not brackets)
—Interligamentary injections
—Prophylactic cleaning where bleeding is anticipated
  • Tonsillectomy and/or adenoidectomy
  • Bronchoscopy with a rigid bronchoscope
  • Surgical operations that involve the respiratory mucosa
  • Sclerotherapy for esophageal varices
  • Esophageal strictures dilatation
  • Endoscopic retrograde cholangiography with biliary obstruction
  • Biliary tract surgery
  • Surgical operations that involve intestinal mucosa
  • Prostate surgery
  • Cystoscopy
  • Urethral dilation

Antibiotic regimens
  • The most recent guideline recommendations simplified the antibiotic regimens.31
  • Preprocedure antibiotics have replaced the previously common practice of pre- and postprocedure antibiotics for dental, oral, respiratory tract, and esophageal interventions (see Table 40.1).

---

Box 40.1 Cardiac conditions associated with endocarditis.31

**High risk**
- Prosthetic cardiac valves, including bioprosthesis and homograft valves
- Previous bacterial endocarditis
- Complex cyanotic congenital heart disease (for example, single ventricle states, transposition of the great arteries, tetralogy of Fallot)
- Surgically constructed systemic pulmonary shunts or conduits

**Moderate risk**
- Most other congenital cardiac malformations (except isolated secundum atrial septal defect, for which prophylaxis is not indicated)
- Acquired valvular dysfunction (for example, rheumatic heart disease)
- Hypertrophic cardiomyopathy
- Mitral valve prolapse with valvular regurgitation and/or thickened leaflets

**Negligible risk**
- Isolated secundum atrial septal defect
- Surgical repair of atrial septal defect, ventricular septal defect, or patent ductus arteriosus (without residua beyond six months)
- Previous coronary artery bypass graft surgery
- Mitral valve prolapse without valvular regurgitation
- Physiologic, functional or innocent heart murmurs
- Previous Kawasaki disease without valvular dysfunction
- Previous rheumatic fever without valvular dysfunction
- Cardiac pacemakers (intravascular and epicardial) and implanted defibrillators

---

30 Gersony WM, Hayes CJ, Driscoll DJ et al. Bacterial endocarditis in patients with aortic stenosis, pulmonary stenosis, or ventricular septal defect. Circulation 1993;87(suppl I):121-6. A cohort of patients with congenital heart disease was followed for eight years. The incidence of endocarditis in those with aortic stenosis was 27 per 10,000 person years. This was nearly 35 times the population based rate.


Clemens JD, Ransohoff DF. A quantitative assessment of pre-dental antibiotic prophylaxis for patients with mitral valve prolapse. J Chronic Dis 1984;37:531-44. This decision analysis calculated that penicillin prophylaxis in older patients with mitral valve prolapse would cost $1 million for one
- *Streptococcus viridans* (α hemolytic streptococcus) remains the most common cause of endocarditis following these procedures.
- Prophylaxis for genitourinary and gastrointestinal procedures is aimed at coverage for *Enterococcus faecium*. Parenteral regimens are generally preferred.

### Table 40.1 Endocarditis prophylaxis for dental, oral, respiratory tract, or esophageal procedures.\(^{31}\)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard general prophylaxis</strong></td>
<td>Amoxicillin 2.0 g PO 1 h before the procedure</td>
</tr>
<tr>
<td><strong>Unable to take oral medications</strong></td>
<td>Ampicillin 2.0 g IM or IV 30 min before the procedure</td>
</tr>
<tr>
<td><strong>Allergic to penicillin</strong></td>
<td>Clindamycin 600 mg PO 1 h before the procedure</td>
</tr>
<tr>
<td>or</td>
<td>Cephalexin 2.0 g PO 1 h before the procedure</td>
</tr>
<tr>
<td>or</td>
<td>Cefadroxil 2.0 g PO 1 h before the procedure</td>
</tr>
<tr>
<td>or</td>
<td>Azithromycin 500 mg PO 1 h before the procedure</td>
</tr>
<tr>
<td>or</td>
<td>Clarithromycin 500 mg PO 1 h before the procedure</td>
</tr>
<tr>
<td><strong>Allergic to penicillin and unable to take oral medications</strong></td>
<td>Clindamycin 600 mg IV within 30 min before the procedure</td>
</tr>
<tr>
<td>or</td>
<td>Cefazolin 1.0 g IM or IV within 30 min before the procedure</td>
</tr>
</tbody>
</table>

year of life saved. In younger patients, the use of parenteral penicillin could in fact result in a net loss of life due to deaths from anaphylaxis.
41 Venous thromboembolism
Lloyd Wasserman

Epidemiology
Incidence
- Venous thromboembolism (VTE) refers to both deep venous thrombosis (DVT) and pulmonary embolism (PE), two phenomena that are part of the same disease.
- Age adjusted annual incidence of a first episode of venous thrombosis and/or embolism is 0.12% (about one episode per 1000 people per year). ¹

Risk factors for VTE: Virchow’s triad
1. Venous stasis: immobility, heart failure, postphlebitic changes, pregnancy, or venous compression by neoplasm
2. Trauma: including surgery and childbirth
3. Hypercoagulability: malignancy, myeloproliferative disorders disseminated intravascular coagulation, oral contraceptives, hormone replacement therapy, family history of DVT, or primary thrombophilia

Risk of DVT in High Risk Subgroups without Prophylaxis ²
- Acute stroke 56%
- Multiple trauma 50%
- Hip fracture 45%
- General surgical 32%
- Acute MI 22%

Ethnicity, VTE, and the Most Common Thrombophilias. ³

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Relative risk of VTE ²</th>
<th>Prevalence of factor V Leiden ²</th>
<th>Prevalence of factor II G20210A ³</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>1.0</td>
<td>5.3</td>
<td>2.3</td>
</tr>
<tr>
<td>African American</td>
<td>1.3</td>
<td>1.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.6</td>
<td>2.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>0.3</td>
<td>0.5</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Risk of VTE in Patients with Thrombophilia

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Odds ratio ⁵–⁸</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden</td>
<td>10</td>
</tr>
<tr>
<td>AT III deficiency</td>
<td>43</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>31</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>36</td>
</tr>
<tr>
<td>Factor II G20210A</td>
<td>3</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>3</td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td>9</td>
</tr>
</tbody>
</table>

- About 50% of carriers of protein C, protein S, and AT III deficiencies will have had a VTE by the ages of 36, 26, and 21, respectively. ⁹
Patients with cancer – particularly of the lung, breast, pancreas, and stomach – have a higher incidence of VTE than those without cancer. The annual VTE rate of women with breast cancer is 0.31%; chemotherapy increases this risk to 4.5%.10

The odds ratio of VTE among oral contraceptive (OC) users compared to non-users is 4.4, corresponding to an absolute risk increase of about 1–2 excess events per 10 000 patient years.11 The odds ratio of VTE in current users of estrogen replacement therapy is 2.1. The absolute risk increase is about 1–2 excess events per 10 000 patient years.12

**Diagnosis**

**History and physical exam**

**Differential diagnosis of leg swelling**

- Heart failure, cirrhosis, nephrotic syndrome, deep venous insufficiency, cellulitis, leg held chronically in dependent position (as in rest pain of arterial disease), dissection or rupture of a popliteal cyst (Baker’s cyst), lymphedema, hematoma, ruptured calf muscle, and tumor.

**Differential diagnosis of calf pain**

- Muscle strain or tear, cellulitis, hematoma, claudication, pseudoclaudication (spinal stenosis), superficial thrombophlebitis, dissection or rupture of popliteal cyst, and tumor.

**A clinical prediction rule for DVT in patients presenting with leg pain or swelling**13

- For each of the features below add 1 point.
  - Active cancer
  - Paresis or recent plaster immobilization of leg
  - Recently bedridden >3 days or surgery in the last four weeks
  - Entire leg swollen
  - Calf circumference 3 cm greater than the unaffected side
  - Pitting edema (greater in the symptomatic leg)
  - Non-varicose collateral superficial veins
  - If an alternative diagnosis is at least as likely as DVT, subtract 2 points

<table>
<thead>
<tr>
<th>Score</th>
<th>Pretest probability of DVT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥3</td>
<td>75</td>
</tr>
<tr>
<td>1–2</td>
<td>17</td>
</tr>
<tr>
<td>≤0</td>
<td>3</td>
</tr>
</tbody>
</table>

**Symptoms and signs of chronic venous insufficiency**

- Chronic venous insufficiency is the most common cause of unilateral leg swelling.
- Patients present with pruritus, scaly rash, hyperpigmentation, and varicose veins.
Most cases of deep venous insufficiency probably occur after asymptomatic DVT. Ultrasound evidence of venous insufficiency can first be seen from days to years after DVT.

Venous insufficiency ulcers are most often in the medial malleolar area. The ulcer base consists of moist granulation tissue. The pain of venous ulcers is less severe than that of arterial ulcers and is relieved by elevating the leg.

**Diagnostic testing**

**D-dimer assay**

- The D-dimer whole blood assay is more accurate than the latex assay and less expensive than the ELISA. It has poor specificity (many false positives) in cancer patients. Even in non-cancer patients, this test is inferior to ultrasound.

**D-Dimer Whole Blood Assay**

<table>
<thead>
<tr>
<th>Patient subset</th>
<th>Sens (%)</th>
<th>Spec (%)</th>
<th>+ LR</th>
<th>− LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>With cancer</td>
<td>86</td>
<td>48</td>
<td>1.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Without cancer</td>
<td>82</td>
<td>82</td>
<td>4.6</td>
<td>0.2</td>
</tr>
</tbody>
</table>

- The test may be less sensitive if the blood sample is sent to the lab in a tube with citrate instead of being done at the bedside.

**Compression ultrasonography**

- The best non-invasive method of diagnosing symptomatic DVT. Sensitivity is 96% for proximal and 80% for distal DVT; specificity is 96%.
- Screening asymptomatic high risk patients is not useful due to a high number of false positive and false negative results.
- A negative test does not rule out thrombus distal to the popliteal vein. These thrombi are probably not responsible for clinically significant pulmonary emboli; however, they may propagate to the popliteal veins, at which point there is risk for embolization.

**Contrast venography**

- Venogram is the gold standard for diagnosis of DVT. Complications include DVT, superficial phlebitis, and contrast nephropathy. Indications include:
  - when ultrasound results in a limited study
  - when the risk of anticoagulation requires a very high post-test probability (for example, in a patient with a bleeding diathesis)
  - when the venous ultrasound is negative in a patient with a high pretest probability of DVT
  - when the venous ultrasound is negative in a patient with documented PE who is a candidate for vena cava filter placement. Lower extremity venography is positive in 80% of patients with PE.
  - prior to thrombolytic therapy.

---

**D-dimer whole blood assay**

A conjugate of monoclonal antibodies binds to red blood cells and to crosslinked fibrin degradation products (FDPs) that contain D-dimer. When it is added to whole blood the agglutination of red blood cells is visible if crosslinked FDPs are present in concentrations greater than 120 ng/ml.


15 Farrell S, Hayes T, Shaw M. A negative SimpliRED D-dimer assay result does not exclude the diagnosis of deep vein thrombosis or pulmonary embolus in emergency department patients. Ann Emerg Med. 2000;35:121–5. In this study, sensitivity was only 65%.


17 Girard P, Musset D, Parent F et al. High prevalence of detectable deep venous thrombosis in patients with acute pulmonary embolism. Chest. 1999;116:903–8. Cohort of 228 patients with PE confirmed by angiography. 81.7% of patients who underwent lower extremity venography in ≤24 hours had a positive venogram. Lower sensitivities in previous studies reflect use of ultrasound, which is not sensitive for asymptomatic DVT.
Testing for hypercoagulability (thrombophilia)

- **Whom to test**: patients with VTE who are < age 45, have a family history of thromboembolism, a history of recurrent thrombosis or embolism, thrombosis in an unusual site, or recurrent superficial thrombophlebitis.
- **Timing of the test**: it is best to test patients > 1 month after anticoagulation has been discontinued and not while the patient is taking oral contraceptives or is pregnant. Heparin, warfarin, and the presence of thrombus alter serum levels of components of the coagulation cascade.
- **What to test for**:
  - Protein C
  - Anticardiolipin antibodies
  - Protein S
  - Lupus anticoagulant
  - Antithrombin III
  - Homocysteine
  - Factor V Leiden
  - PT/PTT
  - Hemogram

Screening for cancer

- There is an increased incidence of malignancy in patients with VTE; however, there is no evidence to support routine extensive work up for occult malignancy. 18
- **Appropriate screening for malignancy**: history, physical examination, complete blood count, urinalysis, chest radiograph, and age appropriate cancer screening tests (Pap testing, mammogram, screening for colon cancer, prostate specific antigen) should be performed. Further testing should only be done to evaluate abnormalities detected with the above tests.

Treatment

Primary prevention of DVT in outpatients

There are minimal clinical data regarding primary DVT prophylaxis with anticoagulants for high risk outpatients.

Treatment of PE or proximal DVT

- The patient should be admitted for ≥ 5 days of intravenous heparin or given ≥ 5 days of subcutaneous low molecular weight heparin at home or in the hospital.
- Home therapy should only be given to those who are hemodynamically stable, capable of self administering injections, without major bleeding risk, and without proven or suspected PE. 19,20
- Warfarin should be started concurrently with heparin on the day of diagnosis and continued for 3–6 months with a target INR of 2–3. An INR should be checked every two weeks until stable and then monthly.

Six Weeks v Six Months of Anticoagulation for VTE 21

<table>
<thead>
<tr>
<th>Outcome</th>
<th>6 weeks (%)</th>
<th>6 months (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td>21.5</td>
<td>10.5</td>
</tr>
<tr>
<td>Death</td>
<td>5.0</td>
<td>1.7 (P = NS)</td>
</tr>
<tr>
<td>Major hemorrhage</td>
<td>0.2</td>
<td>1.0 (P = NS)</td>
</tr>
</tbody>
</table>

18 Cornuz J, Pearson SD, Creager MA et al. Importance of findings on the initial evaluation for cancer in patients with symptomatic idiopathic deep vein thrombosis. Ann Intern Med. 1996;125:785–93. Using only history, physical exam, hemogram, and chest radiograph during initial presentation resulted in 16 diagnoses of cancer among 142 patients with idiopathic DVT. During 34 months of follow up, 2.5% of patients with DVT developed cancer, and 2.7% of patients without DVT developed cancer.


20 The Columbus Investigators. Low-molecular weight heparin in the treatment of patients with venous thromboembolism. N Engl J Med 1997;37:57–63. Randomized controlled trial of reviparin v unfractionated heparin in 510 patients. There were no significant differences in rates of recurrence, bleeding, or death.

Six Months vs 24 Months of Anticoagulation for Recurrent VTE

<table>
<thead>
<tr>
<th>Event</th>
<th>6 months (%)</th>
<th>24 months (%)</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td>21</td>
<td>3</td>
<td>8.0</td>
</tr>
<tr>
<td>Death</td>
<td>14</td>
<td>9</td>
<td>1.7</td>
</tr>
<tr>
<td>Major hemorrhage</td>
<td>2.7</td>
<td>8.6</td>
<td>0.3</td>
</tr>
</tbody>
</table>

- Deep venous insufficiency: mild to moderate symptoms occur in 18%, 25%, and 30% of patients at one, two, and five years after DVT. Severe disease occurs in 2.7% of patients at one year and 8.1% at five years.\(^{23}\)
- Phlegmasia caerulea dolens is a rare complication of DVT. The patient has pain and cyanosis and rapidly develops massive, tense edema secondary to total venous occlusion. The mortality rate is 20–40%. Gangrene occurs in 40–60%.\(^{24}\)

Management of patients with VTE and thrombophilia
- Patients with deficiency of protein C, protein S, or antithrombin III, and homozygotes for factor V Leiden should receive lifelong anticoagulation.
- There is not consensus on management of heterozygotes for factor V Leiden, patients with factor II G20210A mutation, patients with anticardiolipin antibody, or patients with hyperhomocysteinemia.
- Prothrombin time and INR may not be reliable tests for monitoring warfarin therapy in patients with the lupus anticoagulant.

Isolated or suspected calf DVT
- Anticoagulation may be withheld if serial duplex scans are performed every three days for ~12 days and then at three and six months to rule out propagation to the popliteal vein, which would require anticoagulation.
- In outpatients, it is safe to do only one follow-up ultrasound 5–7 days later.\(^{25}\) Alternatively, the patient may be treated with anticoagulation as above.

Management after recurrent DVT or PE
- Coumadin should be given for life, with a target INR of 2–3.

Inferior vena caval (IVC) filter
- Indicated in patients who cannot receive anticoagulants, have failed anticoagulant therapy, or whose current medical status predicts a poor outcome in the event of PE.

Outcomes with IVC Filter\(^{26}\)

<table>
<thead>
<tr>
<th>Event</th>
<th>IVC filter (%)</th>
<th>No IVC filter (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 days after placement of filter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PE</td>
<td>1.1</td>
<td>4.8</td>
</tr>
<tr>
<td>Major bleed</td>
<td>4.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Death</td>
<td>2.5</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Chronic venous insufficiency

- **Compression stockings**, 30–40 mmHg, if tolerated, may retard loss of skin integrity and improve healing of pre-existing ulcers. They are recommended for all patients with DVT.\textsuperscript{27} They should be worn after several days of treatment with heparin. Compression stockings are contraindicated in patients with coexisting arterial disease. The stockings should be put on every day when the patient gets out of bed, for life.

Prevention of Deep Venous Insufficiency after VTE with Compression Stockings\textsuperscript{27}

<table>
<thead>
<tr>
<th>Outcome after 5 years</th>
<th>No stockings (%)</th>
<th>Stockings (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild–mod post-thrombotic syndrome</td>
<td>47</td>
<td>20</td>
</tr>
<tr>
<td>Severe post-thrombotic syndrome</td>
<td>23</td>
<td>11</td>
</tr>
</tbody>
</table>

- **Horse-chestnut seed extract** provides reduction of edema comparable to compression stockings. It is presumed to work by inhibiting capillary permeability.\textsuperscript{28}
- **Elevating the legs** above the level of the heart every three hours for 20 minutes at a time may be useful. Alternatively, the foot of the patient’s bed can be placed on 3-inch blocks.

**Chronic stasis dermatitis**

- Hydrocortisone cream 1% may be used.
- For acute flares triamcinolone ointment 0.1% may be used for two weeks.

Table 41.1 Agents for venous thromboembolic disease.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage form</th>
<th>Usual dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalteparin (Fragmin)</td>
<td>2500 U prefilled syringe</td>
<td>120 U/kg SQ bid ≥ 5 days for initial treatment of DVT</td>
</tr>
<tr>
<td></td>
<td>5000 U prefilled syringe</td>
<td></td>
</tr>
<tr>
<td>Enoxaparin (Lovenox)</td>
<td>3000, 4000, 6000, 8000, 10000 U syringe</td>
<td>100 U/kg SQ bid ≥ 5 days for initial treatment of DVT</td>
</tr>
<tr>
<td>Warfarin (Coumadin)</td>
<td>1, 2, 2.5, 3, 4, 5, 6, 7.5, 10 mg</td>
<td>See Chapter 3</td>
</tr>
</tbody>
</table>
### Appendix A 30 Leading causes of death worldwide – 1990

<table>
<thead>
<tr>
<th>Rank</th>
<th>Cause of deaths</th>
<th>Number of deaths $(\times 10^3)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ischemic heart disease</td>
<td>6260</td>
</tr>
<tr>
<td>2</td>
<td>Cerebrovascular disease</td>
<td>4381</td>
</tr>
<tr>
<td>3</td>
<td>Lower respiratory infections</td>
<td>4299</td>
</tr>
<tr>
<td>4</td>
<td>Diarrheal diseases</td>
<td>2946</td>
</tr>
<tr>
<td>5</td>
<td>Perinatal disorders</td>
<td>2443</td>
</tr>
<tr>
<td>6</td>
<td>Chronic obstructive pulmonary disease</td>
<td>2211</td>
</tr>
<tr>
<td>7</td>
<td>Tuberculosis (HIV negative only)</td>
<td>1960</td>
</tr>
<tr>
<td>8</td>
<td>Measles</td>
<td>1058</td>
</tr>
<tr>
<td>9</td>
<td>Road traffic accidents</td>
<td>999</td>
</tr>
<tr>
<td>10</td>
<td>Trachea, bronchus, and lung cancers</td>
<td>945</td>
</tr>
<tr>
<td>11</td>
<td>Malaria</td>
<td>856</td>
</tr>
<tr>
<td>12</td>
<td>Self-inflicted injuries</td>
<td>786</td>
</tr>
<tr>
<td>13</td>
<td>Cirrhosis of the liver</td>
<td>779</td>
</tr>
<tr>
<td>14</td>
<td>Stomach cancer</td>
<td>752</td>
</tr>
<tr>
<td>15</td>
<td>Congenital anomalies</td>
<td>589</td>
</tr>
<tr>
<td>16</td>
<td>Diabetes mellitus</td>
<td>571</td>
</tr>
<tr>
<td>17</td>
<td>Violence</td>
<td>563</td>
</tr>
<tr>
<td>18</td>
<td>Tetanus</td>
<td>542</td>
</tr>
<tr>
<td>19</td>
<td>Nephritis and nephrosis</td>
<td>536</td>
</tr>
<tr>
<td>20</td>
<td>Drowning</td>
<td>504</td>
</tr>
<tr>
<td>21</td>
<td>War injuries</td>
<td>502</td>
</tr>
<tr>
<td>22</td>
<td>Liver cancer</td>
<td>501</td>
</tr>
<tr>
<td>23</td>
<td>Inflammatory heart diseases</td>
<td>495</td>
</tr>
<tr>
<td>24</td>
<td>Colon and rectum cancers</td>
<td>472</td>
</tr>
<tr>
<td>25</td>
<td>Protein energy malnutrition</td>
<td>372</td>
</tr>
<tr>
<td>26</td>
<td>Esophagus cancer</td>
<td>358</td>
</tr>
<tr>
<td>27</td>
<td>Pertussis</td>
<td>347</td>
</tr>
<tr>
<td>28</td>
<td>Rheumatic heart disease</td>
<td>340</td>
</tr>
<tr>
<td>29</td>
<td>Breast cancer</td>
<td>322</td>
</tr>
<tr>
<td>30</td>
<td>HIV</td>
<td>312</td>
</tr>
</tbody>
</table>

### Appendix B 15 Leading causes of death, United States – 1998

<table>
<thead>
<tr>
<th></th>
<th>Cases per 100,000 population</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Diseases of the heart</td>
</tr>
<tr>
<td>2.</td>
<td>Malignant neoplasms</td>
</tr>
<tr>
<td>3.</td>
<td>Cerebrovascular diseases</td>
</tr>
<tr>
<td>4.</td>
<td>Chronic obstructive pulmonary diseases</td>
</tr>
<tr>
<td>5.</td>
<td>Accidents and adverse effects</td>
</tr>
<tr>
<td>6.</td>
<td>Pneumonia and influenza</td>
</tr>
<tr>
<td>7.</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>8.</td>
<td>Suicide</td>
</tr>
<tr>
<td>9.</td>
<td>Nephritis, nephritic syndrome, and nephrosis</td>
</tr>
<tr>
<td>10.</td>
<td>Chronic liver disease and cirrhosis</td>
</tr>
<tr>
<td>11.</td>
<td>Septicemia</td>
</tr>
<tr>
<td>12.</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>13.</td>
<td>Homicide and legal intervention</td>
</tr>
<tr>
<td>14.</td>
<td>Atherosclerosis</td>
</tr>
<tr>
<td>15.</td>
<td>Hypertension with or without renal disease</td>
</tr>
</tbody>
</table>

## Appendix C  Estimated new cancer cases and deaths by sex for all sites, United States – 2000*

<table>
<thead>
<tr>
<th>Site</th>
<th>Estimated new cases</th>
<th>Estimated deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Both sexes</td>
<td>Men</td>
</tr>
<tr>
<td>All sites</td>
<td>1220 100</td>
<td>619 700</td>
</tr>
<tr>
<td>Oral cavity and pharynx</td>
<td>30 200</td>
<td>20 200</td>
</tr>
<tr>
<td>Tongue</td>
<td>6900</td>
<td>4500</td>
</tr>
<tr>
<td>Mouth</td>
<td>10 900</td>
<td>6500</td>
</tr>
<tr>
<td>Pharynx</td>
<td>8200</td>
<td>5900</td>
</tr>
<tr>
<td>Other oral cavity</td>
<td>4200</td>
<td>3300</td>
</tr>
<tr>
<td>Digestive system</td>
<td>226 600</td>
<td>117 600</td>
</tr>
<tr>
<td>Esophagus</td>
<td>12 300</td>
<td>9200</td>
</tr>
<tr>
<td>Stomach</td>
<td>21 500</td>
<td>13 400</td>
</tr>
<tr>
<td>Small intestine</td>
<td>4700</td>
<td>2300</td>
</tr>
<tr>
<td>Colon</td>
<td>93 800</td>
<td>43 400</td>
</tr>
<tr>
<td>Rectum</td>
<td>36 400</td>
<td>20 200</td>
</tr>
<tr>
<td>Anus, anal canal and anorectum</td>
<td>3400</td>
<td>1400</td>
</tr>
<tr>
<td>Liver and intrahepatic bile duct</td>
<td>13 300</td>
<td>10 000</td>
</tr>
<tr>
<td>Gallbladder and other biliary</td>
<td>6900</td>
<td>2900</td>
</tr>
<tr>
<td>Pancreas</td>
<td>28 300</td>
<td>13 700</td>
</tr>
<tr>
<td>Other digestive organs</td>
<td>4000</td>
<td>1100</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>179 400</td>
<td>101 500</td>
</tr>
<tr>
<td>Larynx</td>
<td>10 100</td>
<td>8100</td>
</tr>
<tr>
<td>Lung and bronchus</td>
<td>164 100</td>
<td>89 500</td>
</tr>
<tr>
<td>Other respiratory organs</td>
<td>5200</td>
<td>3900</td>
</tr>
<tr>
<td>Bones and joints</td>
<td>2500</td>
<td>1500</td>
</tr>
<tr>
<td>Soft tissue (including heart)</td>
<td>8100</td>
<td>4300</td>
</tr>
<tr>
<td>Skin (non-basal, non-squamous)</td>
<td>56 900</td>
<td>34 100</td>
</tr>
<tr>
<td>Melanomas</td>
<td>47 700</td>
<td>27 300</td>
</tr>
<tr>
<td>Other non-epithelial skin</td>
<td>9200</td>
<td>6800</td>
</tr>
<tr>
<td>Breast</td>
<td>184 200</td>
<td>1400</td>
</tr>
<tr>
<td>Genital system</td>
<td>265 900</td>
<td>188 400</td>
</tr>
<tr>
<td>Uterine cervix</td>
<td>12 800</td>
<td>—</td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>36 100</td>
<td>—</td>
</tr>
<tr>
<td>Ovary</td>
<td>23 100</td>
<td>—</td>
</tr>
<tr>
<td>Vulva</td>
<td>3400</td>
<td>—</td>
</tr>
<tr>
<td>Vagina and other female genital</td>
<td>2100</td>
<td>—</td>
</tr>
<tr>
<td>Prostate</td>
<td>180 400</td>
<td>180 400</td>
</tr>
<tr>
<td>Testis</td>
<td>6900</td>
<td>6900</td>
</tr>
<tr>
<td>Penis and other male genital</td>
<td>1100</td>
<td>1100</td>
</tr>
<tr>
<td>Urinary system</td>
<td>86 700</td>
<td>58 600</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>53 200</td>
<td>38 300</td>
</tr>
</tbody>
</table>
## APPENDIX

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney and renal pelvis</td>
<td>31,200</td>
<td>18,800</td>
<td>12,400</td>
<td>11,900</td>
<td>7,300</td>
<td>4,600</td>
</tr>
<tr>
<td>Ureter and other urinary organs</td>
<td>2,300</td>
<td>1,500</td>
<td>800</td>
<td>500</td>
<td>300</td>
<td>200</td>
</tr>
<tr>
<td>Eye and orbit</td>
<td>2,200</td>
<td>1,200</td>
<td>1,000</td>
<td>200</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Brain and other nervous system</td>
<td>16,500</td>
<td>9,500</td>
<td>7,000</td>
<td>13,200</td>
<td>7,100</td>
<td>5,900</td>
</tr>
<tr>
<td>Endocrine system</td>
<td>20,200</td>
<td>5,600</td>
<td>14,600</td>
<td>2,100</td>
<td>1,000</td>
<td>1,100</td>
</tr>
<tr>
<td>Thyroid</td>
<td>18,400</td>
<td>4,700</td>
<td>13,700</td>
<td>1,200</td>
<td>500</td>
<td>700</td>
</tr>
<tr>
<td>Other endocrine</td>
<td>1,800</td>
<td>900</td>
<td>900</td>
<td>900</td>
<td>500</td>
<td>700</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>62,300</td>
<td>35,900</td>
<td>26,400</td>
<td>27,500</td>
<td>14,400</td>
<td>13,100</td>
</tr>
<tr>
<td>Hodgkin’s disease</td>
<td>7,400</td>
<td>4,200</td>
<td>3,200</td>
<td>1,400</td>
<td>700</td>
<td>700</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>54,900</td>
<td>31,700</td>
<td>23,200</td>
<td>26,100</td>
<td>13,700</td>
<td>12,400</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>13,600</td>
<td>7,300</td>
<td>6,300</td>
<td>11,200</td>
<td>5,800</td>
<td>5,400</td>
</tr>
<tr>
<td>Leukemia</td>
<td>30,800</td>
<td>16,900</td>
<td>13,900</td>
<td>21,700</td>
<td>12,100</td>
<td>9,600</td>
</tr>
<tr>
<td>Acute lymphocytic leukemia</td>
<td>3,200</td>
<td>1,800</td>
<td>1,400</td>
<td>1,300</td>
<td>700</td>
<td>600</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td>8,100</td>
<td>4,600</td>
<td>3,500</td>
<td>4,800</td>
<td>2,800</td>
<td>2,000</td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>9,700</td>
<td>4,800</td>
<td>4,900</td>
<td>7,100</td>
<td>3,900</td>
<td>3,200</td>
</tr>
<tr>
<td>Chronic myeloid leukemia</td>
<td>4,400</td>
<td>2,600</td>
<td>1,800</td>
<td>2,300</td>
<td>1,300</td>
<td>1,000</td>
</tr>
<tr>
<td>Other leukemia</td>
<td>5,400</td>
<td>3,100</td>
<td>2,300</td>
<td>6,200</td>
<td>3,400</td>
<td>2,800</td>
</tr>
<tr>
<td>Other and unspecified primary sites</td>
<td>34,000</td>
<td>15,700</td>
<td>18,300</td>
<td>36,600</td>
<td>18,500</td>
<td>18,100</td>
</tr>
</tbody>
</table>

*(American Cancer Society, 2000).*
# Appendix D  Centers for disease control notifiable diseases, United States – 1998

<table>
<thead>
<tr>
<th>No.</th>
<th>Disease Description</th>
<th>Reported cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Chlamydia (<em>C. trachomatis</em> genital infection)</td>
<td>604,420</td>
</tr>
<tr>
<td>2.</td>
<td>Gonorrhea</td>
<td>355,642</td>
</tr>
<tr>
<td>3.</td>
<td>Varicella (chicken pox)</td>
<td>82,455</td>
</tr>
<tr>
<td>4.</td>
<td>AIDS</td>
<td>46,521</td>
</tr>
<tr>
<td>5.</td>
<td>Salmonellosis</td>
<td>43,694</td>
</tr>
<tr>
<td>6.</td>
<td>Syphilis, total (all stages)</td>
<td>37,977</td>
</tr>
<tr>
<td>7.</td>
<td>Shigellosis</td>
<td>23,626</td>
</tr>
<tr>
<td>8.</td>
<td>Hepatitis A</td>
<td>23,229</td>
</tr>
<tr>
<td>9.</td>
<td>Tuberculosis</td>
<td>18,361</td>
</tr>
<tr>
<td>10.</td>
<td>Lyme disease</td>
<td>16,801</td>
</tr>
<tr>
<td>11.</td>
<td>Hepatitis B</td>
<td>10,258</td>
</tr>
<tr>
<td>12.</td>
<td>Pertussis (whooping cough)</td>
<td>7,405</td>
</tr>
<tr>
<td>13.</td>
<td>Rabies, animal</td>
<td>7,259</td>
</tr>
<tr>
<td>14.</td>
<td>Syphilis, primary and secondary</td>
<td>6,993</td>
</tr>
<tr>
<td>15.</td>
<td>Cryptosporidiosis</td>
<td>3,793</td>
</tr>
<tr>
<td>16.</td>
<td>Hepatitis C/non-A, non-B</td>
<td>3,518</td>
</tr>
<tr>
<td>17.</td>
<td><em>Escherichia coli</em> O157:H7</td>
<td>3,161</td>
</tr>
<tr>
<td>18.</td>
<td>Meningococcal disease</td>
<td>2,725</td>
</tr>
<tr>
<td>19.</td>
<td>Malaria</td>
<td>1,611</td>
</tr>
<tr>
<td>20.</td>
<td>Legionellosis</td>
<td>1,355</td>
</tr>
<tr>
<td>21.</td>
<td><em>Haemophilus influenzae</em>, invasive</td>
<td>1,194</td>
</tr>
<tr>
<td>22.</td>
<td>Syphilis, congenital (age &lt; 1 year)</td>
<td>801</td>
</tr>
<tr>
<td>23.</td>
<td>Mumps</td>
<td>666</td>
</tr>
<tr>
<td>24.</td>
<td>Typhoid fever</td>
<td>375</td>
</tr>
<tr>
<td>25.</td>
<td>Rocky Mountain spotted fever</td>
<td>365</td>
</tr>
<tr>
<td>26.</td>
<td>Rubella (German measles)</td>
<td>364</td>
</tr>
<tr>
<td>27.</td>
<td>Chancroid</td>
<td>189</td>
</tr>
<tr>
<td>28.</td>
<td>Toxic shock syndrome</td>
<td>138</td>
</tr>
<tr>
<td>29.</td>
<td>Botulism, total</td>
<td>116</td>
</tr>
<tr>
<td>30.</td>
<td>Hansen disease (leprosy)</td>
<td>108</td>
</tr>
<tr>
<td>31.</td>
<td>Measles (rubeola)</td>
<td>100</td>
</tr>
<tr>
<td>32.</td>
<td>Encephalitis, California serogroup viral</td>
<td>97</td>
</tr>
<tr>
<td>33.</td>
<td>Brucellosis</td>
<td>79</td>
</tr>
<tr>
<td>34.</td>
<td>Psittacosis</td>
<td>47</td>
</tr>
<tr>
<td>35.</td>
<td>Tetanus</td>
<td>41</td>
</tr>
<tr>
<td>36.</td>
<td>Encephalitis, St Louis</td>
<td>24</td>
</tr>
<tr>
<td>37.</td>
<td>Trichinosis</td>
<td>19</td>
</tr>
<tr>
<td>38.</td>
<td>Cholera</td>
<td>17</td>
</tr>
<tr>
<td>39.</td>
<td>Plague</td>
<td>9</td>
</tr>
<tr>
<td>40.</td>
<td>Rubella, congenital syndrome</td>
<td>7</td>
</tr>
<tr>
<td>41.</td>
<td>Encephalitis, Eastern equine</td>
<td>4</td>
</tr>
<tr>
<td>42.</td>
<td>Rabies, human</td>
<td>1</td>
</tr>
<tr>
<td>43.</td>
<td>Diphtheria</td>
<td>1</td>
</tr>
<tr>
<td>44.</td>
<td>Poliomyelitis, paralytic</td>
<td>1</td>
</tr>
</tbody>
</table>

Adapted from: *Summary of Notifiable Diseases, United States – 1998. MMWR 1999;47:3.*
# Appendix E  Recommendations for primary and secondary prevention from the US Preventive Services Task Force

## Screening

<table>
<thead>
<tr>
<th>Condition</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Cholesterol</td>
<td>Measure total cholesterol in <em>all men aged 35–65, all women aged 45–65</em>. Unclear if of benefit between ages 65–75. Screen approximately every five years.</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Check blood pressure at least once every two years in <em>all adults, regardless of age</em>.</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>Mammography alone, or mammography with annual screening breast exam every 1–2 years for <em>all women aged 50–69</em>. Unclear if of benefit in women 40–49 or 70 and older.</td>
</tr>
<tr>
<td>Colorectal Cancer</td>
<td>Fecal occult blood testing every year, or flexible sigmoidoscopy every 3–5 years for <em>all patients 50 or older</em>. There is insufficient evidence to argue for or against routine screening with digital rectal exam, barium enema, or colonoscopy.</td>
</tr>
<tr>
<td>Cervical Cancer</td>
<td>Pap smear should <em>begin at the age when patient becomes sexually active</em> and be performed every three years.</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>Routine screening with digital rectal exam, prostate specific antigen, or transrectal ultrasound is <em>not recommended</em>.</td>
</tr>
<tr>
<td>Rubella</td>
<td>Routine screening for <em>all women of childbearing age</em> with vaccination offered to all susceptible patients.</td>
</tr>
<tr>
<td>HIV</td>
<td>All patients at <em>increased risk</em> should be screened.</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Serologic testing of <em>high risk individuals</em>.</td>
</tr>
<tr>
<td>Gonorrhea</td>
<td>Screening of <em>high risk women</em> w culture or non-culture test.</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>Screening of <em>high risk women</em> w culture or non-culture test.</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Screening with PPD testing is recommended for <em>asymptomatic high risk persons of all ages</em>.</td>
</tr>
<tr>
<td>Problem Drinking</td>
<td>Screen <em>all adults</em> by use of a careful history or use of the CAGE or AUDIT questionnaires.</td>
</tr>
</tbody>
</table>

## Vaccination

<table>
<thead>
<tr>
<th>Condition</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td><em>All patients over 65</em> or in high risk groups. Give every year.</td>
</tr>
<tr>
<td>Streptococcus</td>
<td><em>All patients over 65</em> or in high risk groups. Give once. Consider revaccination after five years in high risk patients.</td>
</tr>
<tr>
<td>Pneumoniae</td>
<td>For <em>all patients not previously immunized</em> give primary Td at 0,2, and 8–14 months. Give <em>all patients</em> a Td booster once every 10 years.</td>
</tr>
<tr>
<td>Tetanus</td>
<td><em>All persons born after 1956</em> who lack evidence of immunity to measles or young adults in a congregate setting (for example, college).</td>
</tr>
<tr>
<td>MMR</td>
<td><em>All young adults not previously vaccinated</em> and <em>all high risk patients</em> (e.g. for example, injection drug users, patients having unprotected sex). Give three vaccinations at 0,1, and 6 months.</td>
</tr>
<tr>
<td>Hep B vaccine</td>
<td><em>All young adults not previously vaccinated</em> and <em>all high risk patients</em> (e.g. for example, injection drug users, patients having unprotected sex). Give three vaccinations at 0,1, and 6 months.</td>
</tr>
</tbody>
</table>
Hep A vaccine  *People in endemic areas, gay men, injection drug users.* Give vaccine at 0 and 6–12 months.

**Topics for counseling**

**Smoking Cessation**  Counsel *all persons who use tobacco products.*

**Exercise**  Counsel *all patients* to promote regular physical activity.

**Diet**  Counsel *all patients* to reduce dietary intake of fat (especially saturated fat), and to maintain caloric balance. Emphasize fruits, vegetables, and grain products containing fiber. There is not good evidence that counseling about dietary salt restriction is effective.

**Sexually Transmitted Disease**  *All patients* should be counseled about risk factors and effective measures to reduce risk of infection.

**Skin Cancer**  Counsel *high risk individuals* regarding sun avoidance and use of protective clothing.

**Hormone Replacement Therapy**  Counsel *all menopausal and postmenopausal women* about potential risks and benefits of hormone prophylaxis.

**Motor Vehicle Injuries**  Counsel *all patients* to use seatbelts, to wear helmets when on a motorcycle, and refrain from driving when under the influence of alcohol or drugs.

Glossary

Evidence-based medicine: the use of current best evidence from research in the care of individual patients.

Diagnosis

Sensitivity (or true positive rate): the percentage of patients with disease who test positive. Sensitivity quantifies the ability of a diagnostic test to detect disease. Sensitivity is about people with disease. False negatives (disease that is missed) hurt sensitivity (sensitivity + false negative rate = 100%).

Specificity (or true negative rate): the percentage of patients without disease who test negative. Specificity quantifies the ability of a diagnostic test to ascertain the absence of disease. Specificity is about people without disease. False positives (mislabeled patients) hurt specificity (specificity + false positive rate = 100%).

Likelihood ratio (LR): the likelihood that a given test result would be seen in someone with as opposed to someone without the disease in question. Likelihood ratios quantify the degree to which a test is positive or negative. A likelihood ratio of >1 means the result is “positive”, i.e. increases the probability that the disease is present. A likelihood ratio of <1 decreases the probability that the disease is present. A likelihood ratio of 1 means that the test result is indeterminate: it does not distinguish between the sick and the well.

For any particular test result, the likelihood ratio = probability of that result in a diseased person / probability of that result in a non-diseased person

For a test with only two outcomes, the LR of a positive result is simply: sensitivity / specificity

For the same test, the LR of a negative result would be: 1 — sensitivity / specificity


<table>
<thead>
<tr>
<th>Heart failure</th>
<th>No heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive electrocardiogram*</td>
<td>90 (.94)</td>
</tr>
<tr>
<td>Negative electrocardiogram</td>
<td>6 (.06)</td>
</tr>
<tr>
<td>96 (1.00)</td>
<td>438 (1.00)</td>
</tr>
</tbody>
</table>

*Atrial fibrillation, prior MI, left ventricular hypertrophy, bundle branch block, or left axis deviation

Prevalence = 96/534 = .18
Sensitivity = 90/96 = .94 Specificity = 269/438 = .61 Positive predictive value = 90/259 = .35
False negative rate = .06 False positive rate = .39 Negative predictive value = 269/275 = .98

Likelihood ratio for a positive ECG = .94/.39 = 2.4
(“A person with heart failure is 2.4 times as likely to have a positive ECG as a person without heart failure.”)

Likelihood ratio for negative ECG = .06/.61 = .10
(“A person with heart failure is one tenth as likely to have a normal ECG as a person without heart failure.”)

Note: Likelihood ratios refer not to tests but to individual test results. A test with several possible degrees of abnormality (like many imaging studies and blood tests) has a different likelihood ratio associated with each result.
**Example:** mammography in the diagnosis of breast cancer in women ≥ 50

<table>
<thead>
<tr>
<th>Mammogram result</th>
<th>Likelihood ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>0.27</td>
</tr>
<tr>
<td>Additional evaluation needed</td>
<td>26.3</td>
</tr>
<tr>
<td>Suspicious for malignancy</td>
<td>30.8</td>
</tr>
<tr>
<td>Malignant</td>
<td>∞</td>
</tr>
</tbody>
</table>

**Therapy**

**Relative risk (RR):** ratio of adverse events in an intervention group compared with a control group.

\[
\text{Relative risk} = \frac{\text{event rate in the intervention group}}{\text{event rate in the control group}}
\]

**Relative risk reduction (RRR):** the proportional reduction in rates of bad outcomes between intervention and control participants. An impressive sounding RRR can be clinically trivial if the disease is rare. RRR is commonly used in drug advertising.

\[
\text{RRR} = \frac{\text{event rate in the control group} - \text{event rate in the intervention group}}{\text{event rate in the control group}}
\]

\[
\text{RRR} = 1 - \text{RR}
\]

**Absolute risk reduction (ARR):** the absolute arithmetic difference in rates of bad outcomes between intervention and control participants. ARR takes event frequency into account and is therefore more clinically meaningful than RRR.

\[
\text{ARR} = \text{event rate in the control group} - \text{event rate in the intervention group}
\]

**Number needed to treat (NNT):** the number of persons who must be treated to achieve one favorable outcome.

\[
\text{NNT} = \frac{1}{\text{ARR}}
\]

**P value (or \( \alpha \) error or Type I error):** the risk of incorrectly concluding that one treatment is superior to another treatment, when in fact the *null hypothesis* is true: the treatments are equivalent. The P value is equivalent to the false positive rate of a diagnostic test. A P value of < .05 is usually taken to mean that the observed difference between two treatments is statistically significant (unlikely to have been caused by chance).

**95% confidence interval:** if the study is unbiased, there is a 95% chance that this interval includes the true effect size.


Patients taking lovastatin: 3304

Acute major coronary events in lovastatin group: 116 (3.5%)  
Patients taking placebo: 3301

Acute major coronary events in placebo group: 183 (5.5%)

Relative risk: 0.63 (0.035/0.055). “Patients taking lovastatin were 63% as likely as placebo patients to experience an acute major coronary event.”

Relative risk reduction: 0.37 (1 — relative risk). “Patients taking lovastatin were 37% less likely than placebo patients to experience an acute major coronary event.”

Absolute risk reduction: 0.02 (0.055 — 0.035). “Acute major coronary events were prevented in 2% of all patients taking lovastatin.”
Number needed to treat: 50 (1/absolute risk reduction). “One acute major coronary event was prevented for every 50 patients taking lovastatin.”

P value: < .001 (there is less than 1 chance in 1000 that a difference as large as this one would have been observed if lovastatin were equivalent to placebo.)

95% confidence interval for relative risk: 0.50–0.79 (If the study is unbiased, there is a 95% chance that the true relative risk lies between 50% and 79%).

Risk
Questions about risk are usually answered in two ways: the quicker, easier, more bias prone way (case control studies) or the longer, more laborious, more expensive way (cohort studies). Below is a comparison of how the two study designs answer the question: “Does second-hand smoke cause lung cancer?”

**Cohort study:** A prospective, observational (as opposed to experimental) study of risk. A cohort is a group of people with something in common, such as being born between 1890 and 1919 and living in Framingham, Massachusetts. It takes a large number of subjects and lots of time to accumulate enough cases to draw conclusions about risk, even in the case of a “common” disease like lung cancer. Subjects with risk factors are compared to subjects without risk factors in terms of disease incidence. In the example below, none of the women has lung cancer at the beginning of the study. Women with husbands who smoke are compared to women with non-smoking husbands to see if the incidence of lung cancer is higher in the women exposed to second-hand smoke. A relative risk of >1 implies that second-hand smoke is a risk factor for lung cancer.

Relative risk = \( \frac{\text{incidence of disease in the exposed}}{\text{incidence of disease in the unexposed}} = \frac{A}{A+B} / \frac{C}{C+D} \)

**Example:** Cardenas VM et al. Environmental tobacco smoke and lung cancer mortality in the American Cancer Society’s Cancer Prevention Study II. Cancer Causes & Control 1997;8:57–64.

<table>
<thead>
<tr>
<th>Cohort study</th>
<th>Dead from lung cancer</th>
<th>Not dead from lung cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never-smoking women married to smokers</td>
<td>96 (.00084)</td>
<td>a</td>
</tr>
<tr>
<td>Never-smoking women married to non-smokers</td>
<td>54 (.00069)</td>
<td>c</td>
</tr>
<tr>
<td></td>
<td>150</td>
<td>192 084</td>
</tr>
</tbody>
</table>

Relative risk = \( \frac{96/114 286}{54/77 948} = \frac{.00084}{.00069} = 1.2 \) (95% CI = 0.8–1.6)

Note that the 95% confidence interval crosses 1; therefore, the relative risk is not statistically significant.

**Case control study:** A retrospective, observational study of risk. Subjects with disease (cases) are compared to subjects without disease (controls) in terms of their prior exposure to risk factors. In the example below, 651 women already have lung cancer when the 1253 controls and the information on second-hand smoke are sought. Women with cancer are compared to women without cancer in terms of their prior exposure to second-hand smoke. The incidence of lung cancer cannot be determined in a case control study. (How does one know when to stop recruiting controls? There is no reliable denominator.) Therefore, the relative risk formula used in cohort studies cannot be invoked. Risk is approximated in terms of an odds ratio.
Case control studies are especially prone to bias and chance. The 651 women with cancer might have all sorts of things in common. What if a disproportionate number of them live near high tension wires or have red hair or voted for Dukakis in 1988? Almost any aspect of the cases’ lives can be sought out as a risk factor in a case control study. For this reason, many clinicians are skeptical about odds ratios of less than 3. Also, associations between risk and disease uncovered in case control studies must make biological sense.

**Odds:** The probability that an event will happen divided by the probability that it will not happen. A probability of .75 is equivalent to odds of 3 (.75/.25 = 3).

**Odds ratio:** In a case control study, the odds that a case (patient with the disease) is exposed to a risk factor divided by the odds that a control (patient without the disease) is exposed to the risk factor.

\[
\frac{[A/(A+C)+C/(A+C)]}{[B/(B+D)+D/(B+D)]}
\]

which simplifies to... \( \frac{A/C}{B/D} \) or \( \frac{AD}{BC} \)


<table>
<thead>
<tr>
<th>Case control study</th>
<th>Lung cancer (cases)</th>
<th>No lung cancer (controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed to environmental smoke</td>
<td>433 (.67)</td>
<td>a b 766 (.61) 1199</td>
</tr>
<tr>
<td>Not exposed</td>
<td>218 (.33)</td>
<td>c d 487 (.39) 605</td>
</tr>
<tr>
<td></td>
<td>651 (1.00)</td>
<td>1253 (1.00) 1804</td>
</tr>
</tbody>
</table>

**Odds ratio** = \( \frac{\text{odds of lung cancer patients being exposed to smoke}}{\text{odds of controls being exposed to smoke}} \)

\[
= \frac{.67}{.33} \div \frac{.61}{.39} = \frac{1.99}{1.57} = 1.26 \quad (95\% \text{ CI} = 1.04 - 1.54)
\]

Interpretation of the case control study results requires a leap of logic that is epidemiologically sound. Because the odds of previous smoke exposure were 26% greater in lung cancer patients than in controls, the opposite is also presumed to be true: the risk of lung cancer is estimated to be increased by 26% in those who are exposed to smoke.

**Note:** Despite enrolling over 100 times as many subjects, the cohort study has a wider confidence interval than the case control study because of the relatively low number of lung cancer cases in the cohort (150 compared to 651). Although the relative risk and the odds ratio are similar, the relative risk in the cohort study is not statistically significant; the odds ratio in the case control study is statistically significant; the relative risk in the cohort study is not.
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